UNITED STATES DISTRICT COURT
SOUTHERN DISTRICT OF WEST VIRGINIA
CHARLESTON DIVISION

IN RE: ETHICON, INC., PELVIC REPAIR SYSTEM PRODUCTS LIABILITY LITIGATION	**Master File No. 2:12-MD-02327** **MDL 2327** **JOSEPH R. GOODWIN** **U.S. DISTRICT JUDGE**
THIS DOCUMENT RELATES TO: *Wave 4 Cases*	

EXPERT REPORT OF DOUGLAS H. GRIER, M.D.

Report re TVT, TVT-O, TVT-Exact, and TVT-Abbrevo Midurethral Slings

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This report contains a summary of my qualifications, education, training and experience, a statement of my opinions that I have formed to date, the bases for those opinions, and the information I considered in forming my opinions. All of my opinions are based on my education, training, clinical experience, the pertinent medical literature, discussions with colleagues, and other materials I have reviewed. Materials that support my findings and opinions, including documents that I have reviewed, are identified either in this report or are listed in the attached reliance materials list.

All of the opinions I express in this report are held to a reasonable degree of medical and scientific certainty. If I receive additional information after signing this report but before trial, I may form additional or different opinions.

I. Background

a. Education, Training, and Experience

I attended the University of Florida in Gainesville, Florida, graduating with a Bachelor of Science degree in Chemistry with High Honors in 1976. I attended medical school at George Washington University, graduating in 1982. I then did a surgical internship in 1982–1983 at the Portsmouth Naval Hospital in Portsmouth, Virginia. Following my internship, I did a urological residency at the Portsmouth Naval Hospital from 1984–1988. I served as Chief of Urology at Jacksonville Naval Hospital in 1990–1991.

Prior to my residency, I served in Operation Urgent Fury in Grenada in October 1983 and as part of the Multinational Peacekeeping Force in Beirut, Lebanon in 1983–1984. After my residency, I served in Operation Desert Shield and Operation Desert Storm with the 1st Marine Division, stationed in Saudi Arabia and Kuwait in 1990–1991.

I am the President of the Medical Staff at Swedish/Edmonds Hospital in Edmonds, Washington. I also serve as the Chair of Swedish Hospital's Medical Quality Oversight Committee, Chair of the Credentials Committee, Treasurer of the Medical Staff for the Swedish Hospital System, and as a member of the Executive Committee at Swedish Hospital.

I became a Diplomate of the American Board of Urology in 1990 and was recertified in 2010. I am an active member of the American Urological Association, the Washington State Medical Association, the Northwest Urological Society, the Washington State Urology Society, the King County Medical Society, the American Association of Clinical Urologists, the Society of Urodynamics Female Pelvic Medicine & Urogenital Reconstruction, and the International Continence Society.

My curriculum vitae is attached to this report.

b. Clinical Experience & Personal Experience with Stress Urinary Incontinence Treatments

I have a special focus in female pelvic medicine and surgery. Over the course of my career, I have performed various types of native tissue surgery and surgery utilizing mesh, including Ethicon's TVT and TVT-O, TVT-Abbrevo, TVT-Exact and TVT-Secur midurethral slings, AMS Monarch, Uretex by Bard, Vesica In Situ sling, Stamey cystourethropexy, MMK, and Burch procedures. I have also performed robotic sacrocolpopexies, as well as open abdominal sacrocolpopexies. I have also performed various types of native tissue surgeries and surgeries utilizing mesh to treat pelvic organ prolapse and hernias.

c. Teaching & Training Experience Related to Stress Urinary Incontinence

I served as a faculty member at the Ethicon Endosurgical Institute, and as a National Preceptor for Gynecare products, conducting over 300 courses for advanced surgical training of physicians for conditions such as stress urinary incontinence and pelvic organ prolapse. I have lectured to pelvic floor surgeons throughout the United States, Canada, Europe, and China. I have performed research in the field of incontinence and bladder disorders, contributing to studies on the use of TVT abdominal guides, and the TVT world registry published in the Journal of Urology in 2011. I was also an investigator in an FDA trial of a pelvic nerve stimulator for the treatment of urge incontinence.

d. Litigation Consulting Work

During the previous four years, I have testified as an expert witness at trial or by deposition in the following cases:

- Perry v. Ethicon, Inc., et al.—Bakersfield, CA
  - Deposition Testimony on 12/30/14
  - Trial Testimony on 02/17/15, 02/18/15, and 02/19/15
- Daino v. Ethicon and Hill v. Ethicon—
  - Deposition Testimony on 3/29/16
- Freitas v. Ethicon; Ruiz v. Ethicon; Bartlett (Pratt) v. Ethicon; Hankins v. Ethicon; Gray-Wheeler v. Ethicon, Barbara A. Hill v. Ethicon, Daino v. Ethicon,—
  - Deposition Testimony on 3/22/16
- Lambert v. Ethicon; Lenz v. Ethicon; Lewis-McCann v. Ethicon; Majors v. Ethicon—
  - Deposition Testimony on 7/13/16
- In re: Ethicon, Inc. Pelvic Repair System Products Liability Litigation
  - Deposition Testimony on 8/23/16 (Prosima general report)
  - Deposition Testimony on 8/23/16 (TVT Exact general report)
- Conley v. Ethicon; Currie v. Ethicon
  - Deposition Testimony on 8/23/16

I am being compensated $500 per hour for my study and testimony in this case.

II. Stress Urinary Incontinence

a. Definition, Mechanism of Action, and Prevalence

Urinary incontinence is the involuntary leakage of urine, and can take different forms such as urge incontinence, stress incontinence, or mixed incontinence. Urinary incontinence affects up to 50% of women at some point in their lives. (Ford AA, Rogerson L, Cody JD, Ogah J. Mid-urethral sling operations for stress urinary incontinence in women. Cochrane Database Syst Rev. 2015, Issue 7. Art. No.: CD006375. doi: 10.1002/14651858.CD006375.pub3.) Stress Urinary Incontinence ("SUI") is the involuntary leakage of urine during activities such as coughing, sneezing, lifting, laughing, or exercising. (IUGA. Stress Urinary Incontinence – A Guide for Women.) The proposed mechanism of action for the development of stress urinary incontinence is weakening of the pubourethral ligaments and loss of intrinsic sphincter tone.

SUI is diagnosed by bladder questionnaire, examination, cough test, bladder diary, urodynamic studies, and cystoscopy. Pelvic organ prolapse, overactive bladder, and urinary incontinence affect more women than diabetes, heart disease, or arthritis. SUI is a very common condition, and affects at least 10–35% of women. (IUGA. Stress Urinary Incontinence – A Guide for Women; Dooley Y, et al. Urinary incontinence prevalence: results from the National Health and Nutrition Examination Survey. J Urol. 2008 Feb;179(2):665–661.) A recent Cochrane review notes that, of the 50% of women who will experience urinary incontinence at some point in their lives, 30–80% experience SUI. (Ford AA, Rogerson L, Cody JD, Ogah J. Mid-urethral sling operations for stress urinary incontinence in women. Cochrane Database Syst Rev. 2015, Issue 7. Art. No.: CD006375. doi: 10.1002/14651858.CD006375.pub3.) Moderate-to-severe SUI affects women at an increasing rate as they age, and has been reported to affect 6.9% of women 20–39 years old, 17.2% of women 40–59 years old, 23.3% of women aged 60–79 years, and 31.7% of women 80 years or older. (Nygaard I, et al. Prevalence of symptomatic pelvic floor disorders in US women. JAMA. 2008 Sep 17;300(11):1311–1316.) One study estimated that approximately 11% of women will have surgery to treat either SUI or pelvic organ prolapse in their lifetime. (Olsen AL, et al. Epidemiology of surgically managed pelvic organ prolapse and urinary incontinence. Obstet Gynecol. 1997;89:501–506.) Over 200,000 surgeries are performed in the U.S. for the treatment of SUI and pelvic organ prolapse each year. (Gerten KA, et al. Prolapse and incontinence surgery in older women. J Urol. 2008 Jun;179(6):2111–2118.)

b. Risk Factors for Stress Urinary Incontinence

Smoking: Women who smoke are 1.8–2.9 times more likely to develop SUI. (Bump RC, McClish DK. Cigarette smoking and urinary incontinence in women. Am J Obstet Gynecol. 1992 Nov;167(5):1213–1218.) Smoking can lead to COPD, which increases abdominal pressures through chronic coughing.

Obesity: Increasing body mass index correlates to an increase in the symptoms of urinary incontinence and pelvic organ prolapse through the mechanism of increased intravesical pressure and bladder receptor changes. (Hannestad YS, et al. Are smoking and other lifestyle factors associated with female urinary incontinence? The Norwegian EPINCONT Study. Br J Obstet Gynaecol. 2003 Mar;110(3):247–254.) Obese women have a 4.2-fold greater risk of developing SUI compared to women with an average BMI. (ACOG / AUGS Practice Bulletin No. 155; Nov. 2015.)

Menopause: Decreasing serum levels of estrogen are known to increase the incidence of both stress incontinence and integrity of the pubocervical fascia of the vagina by decreasing vascularity and thickness of the tissues. Postmenopausal decreased estrogen levels lead to urogenital atrophy with the increased risk of infections of the urinary tract and changing of the vaginal pH. (Siddighi S, Hardesty JS. Urogynecology & Female Pelvic Reconstructive Surgery. ISBN 0-07-144799-7.)

Pregnancy and Childbirth: Damage sustained to the muscles and nerves of the pelvic floor significantly increases the risk of both stress and urge incontinence and pelvic organ prolapse. A woman with three or more vaginal deliveries has an 11-fold increased risk of pelvic organ prolapse compared to a nulliparous woman. The weight of the infant contributes to prolapse with an increase of 10% per pound weight of the infant. (Siddighi S, Hardesty JS. Urogynecology & Female Pelvic Reconstructive Surgery. ISBN 0-07-144799-7.)

Chronic Constipation and Heavy Lifting: Chronic constipation and heavy lifting cause increased pelvic pressures which lead to increased fascial stress over time.

Race: Increasing incidence of SUI occurs from Asian women < African-American women < Caucasian Women. Caucasian women have the highest risk of pelvic organ prolapse. (Siddighi S, Hardesty JS. Urogynecology & Female Pelvic Reconstructive Surgery. ISBN 0-07-144799-7.)

Age: The mean age for SUI in women is 48 years, for mixed incontinence in women 55 years, and urge incontinence in women is 61 years. The prevalence of incontinence is 39.6 million women as of 2001. (Siddighi S, Hardesty JS. Urogynecology & Female Pelvic Reconstructive Surgery. ISBN 0-07-144799-7.)

Congenital Factors: Women with prolapse tend to have an abundance of the weaker type III collagen in the pubocervical fascia with a higher degree of joint hypermobility with associated collagen vascular disorders. These factors also increase the incidence and severity of prolapse. Collagen vascular diseases have been implicated in the development of SUI and pelvic organ prolapse. (Siddighi S, Hardesty JS. Urogynecology & Female Pelvic Reconstructive Surgery. ISBN 0-07-144799-7.)

Pelvic Organ Prolapse: 62% of women with prolapse also report SUI and 63% of women with stress incontinence have associated prolapse. (Siddighi S, Hardesty JS. Urogynecology & Female Pelvic Reconstructive Surgery. ISBN 0-07-144799-7.)

c. Economic Impact and Impact on Quality of Life

Women who develop urinary incontinence adapt by minimizing activities, wearing incontinence diapers, and by avoiding social interactions and sexual relationships due to fear of embarrassment. (Fultz NH, et al. Burden of stress urinary incontinence for community-dwelling women. Am J Obstet Gynecol. 2003 Nov;189(5):1275–1282.) It has been reported that less than half of women who experience incontinence tell their healthcare providers about their symptoms. (Wu JM, et al. Prevalence and incidence of urinary incontinence in a diverse population of women with noncancerous gynecologic conditions. Female Pelvic Med Reconstr Surg. 2010;16(5):284–289; ACOG / AUGS Practice Bulletin No. 155; Nov. 2015.) The impact of decreased physical activities for fear of incontinence leads to cardiovascular deconditioning, further obesity, and social isolation. The incontinence also increases the incidence of urinary tract infections, which can lead to kidney infections and hospitalizations. The symptoms of SUI can also increase the incidence and severity of depression.

Economic costs of urinary incontinence were estimated to be $32 billion as of 2000, with the cost derived from providing laundry, pads, and absorbent products. The majority of those costs do not come from providing treatment. The November 2015 ACOG/AUGS Practice Bulletin on Urinary Incontinence in Women notes that the "estimated direct cost of urinary incontinence care in the United States is $19.5 billion." (ACOG / AUGS Practice Bulletin No. 155; Nov. 2015.) 62% of women with prolapse also report SUI and 63% of women with stress incontinence have associated prolapse. (Siddighi S, Hardesty JS. Urogynecology & Female Pelvic Reconstructive Surgery. ISBN 0-07-144799-7; Wagner. Economic Costs of Urinary Incontinence. Urology. 1998;51:355–361.) 30% of women will undergo repeat surgery for recurrent prolapse over their lifetime.

III. Treatment Options for SUI

a. Nonsurgical Options for Treatment of Stress Urinary Incontinence

Nonsurgical treatment options for SUI are behavior modifications, including more frequent voiding, incontinence pads or briefs, biofeedback, pelvic-floor muscle exercises, weight reduction, management of fluid intake, smoking cessation, reduced intake of coffee, tea, and carbonated beverages, reduced occupational or recreational activities that require repetitive or chronic straining, and constipation management. Other nonsurgical treatment options include functional electrical stimulation (PTNS) and mechanical devices. (Siddighi S, Hardesty JS. Urogynecology & Female Pelvic Reconstructive Surgery. ISBN 0-07-144799-7; ACOG / AUGS Practice Bulletin No. 155; Nov. 2015.) Only 15–28% of women have their incontinence 100% cured by pelvic-floor muscle training (PFMT), and after a 3–15-year follow-up, 25–50% of women primarily treated with PFMT to try to improve or cure their incontinence will undergo surgery. (Labrie J, et al. Protocol for Physiotherapy OR Tvt Randomised Efficacy Trial (PORTRET): a multicenter randomised controlled trial to assess the cost-effectiveness of the tension free vaginal tape versus pelvic floor muscle training in women with symptomatic moderate to severe stress urinary incontinence. BMC Women's Health. 2009;9:24.)

Pessaries are believed to control SUI symptoms by increasing urethral resistance and supporting the urethra. They "may improve the symptoms of stress and mixed urinary incontinence, but objective evidence regarding their effectiveness has not been reported." (ACOG / AUGS Practice Bulletin No. 155; Nov. 2015.)

The limitations of nonsurgical management options are that they rarely fully restore continence, but rather help cope with the condition. There is no FDA-approved medication for the treatment of SUI. (ICS Fact Sheets: A Background to Urinary and Faecal Incontinence (July 2013); 2013 AUA SUI Patient Guide.)

b. Surgical Options for Treatment of Stress Urinary Incontinence

Because of the limitations of nonsurgical treatment options, surgery is the definitive and long-term treatment for symptomatic SUI. There are over 150 described surgical treatments for SUI. All of these surgeries have shared risks such as hematoma, bladder or bowel injury, lower urinary tract injury, vascular injury, infection, urinary retention, persistent SUI, bleeding, pain, dyspareunia, fistula, and de novo or worsening urge incontinence. (ACOG / AUGS Practice Bulletin No. 155; Nov. 2015.)

i. Native Tissue and Tension Repairs

The primary surgical native tissue and tension repairs include the Kelly plication (introduced in 1912), Pereyra needle urethropexy (introduced in 1959), and abdominal operations for SUI such as the Burch colposuspension (introduced in 1961) and Marshall Marchetti Krantz (MMK) cystourethropexy (introduced in 1949). (Siddighi S, Hardesty JS. Urogynecology & Female Pelvic Reconstructive Surgery. ISBN 0-07-144799-7.)

Retropubic trans-abdominal surgeries (Burch and MMK) when compared to TVT, are less cost-effective, more morbid, have greater operative time, and longer recovery with equal efficacy. (Ward K, et al. Prospective multi-center randomized trial of tension-free vaginal tape and colposuspension as primary treatment for stress incontinence. BMJ. 2002 Jul;325:1–7.) In a randomized controlled trial of TVT versus Burch with five-year follow-up, the procedures had similar patient satisfaction and efficacy, but the TVT group had less voiding dysfunction. (Ward K, Hilton P, on behalf of the UK and Ireland TVT Trial Group. Tension-free vaginal tape versus colposuspension for primary urodynamic stress incontinence: 5-year follow up. BJOG. 2008;115:226–233.) A 2009 Cochrane review of TVT versus Burch reported that TVT appeared to be as effective as the open Burch procedure, but associated with fewer complications, less voiding dysfunction, shorter operative times, and increased safety. (Ogah, J, Cody, JD, Rogerson, L. Minimally invasive synthetic suburethral sling operations for stress urinary incontinence in women. Cochrane Database Syst Rev. 2009, Issue 4. Art. No.: CD006375. doi: 10.1002/14651858.CD006375.pub2.) A meta-analysis of 39 RCTs published in 2010 by Novara, et al. indicated that patients receiving midurethral slings, especially TVT, while having an increased risk of bladder perforation, had significantly higher overall and objective cure rates than did the patients who had a Burch procedure. (Novara G, et al. Updated systematic review and meta-analysis of the comparative data on colposuspensions, pubovaginal slings, and

midurethral tapes in the surgical treatment of female stress urinary incontinence. Eur Urol. 2010 Aug;58(2):218–38.)

Retropubic trans-abdominal surgeries such as the Burch and MMK involve larger incisions, more dissection, are performed as inpatient rather than ambulatory procedures, and have a greater average blood loss than the midurethral sling procedures discussed below. (Chaliha C, Stanton SL. Complications of surgery for genuine stress incontinence. Br J Obstet Gynaecol. 1999 Dec;106(12):1238–45.) Data shows that long-term efficacy following Burch declines with time and plateaus at ten years with 70% cure. One in ten patients needs at least one additional surgery for correction of SUI ten years after undergoing a Burch procedure. (Alcalay. Burch colposuspension: a 10–20 year follow up. Br J Obstet Gynaecol. 1995;102:740–745.) In another long-term study of the Burch procedure, 56% of the patients studied experienced subjectively significant urinary incontinence. (Kjolhede P. Long-term efficacy of Burch colposuspension: a 14–year follow-up study. Acta Obstet Gynecol Scand. 2005, 84:767–772.) In the SISTEr study, 70% of patients undergoing the Burch procedure had treatment failure at two years' follow-up when all criteria were considered. (Albo, ME, et al. Burch Colposuspension versus Fascial Sling to Reduce Urinary Stress Incontinence. N Engl J Med. 2007;356:2143–2155.) In the extended SISTEr trial, between 2–7 years post-op, continence rates dropped from 42% to 13% in patients who had the Burch procedure. (Richter HE, et al. Patient Related Factors Associated with Long-Term Urinary Continence After Burch Colposuspension and Pubovaginal Fascial Sling Surgeries. J Urol. 2012 Aug;188(2):485–489.) A study by Demirci showed comparable trends in decreasing efficacy and late complications. Demirci reported late complications in 220 women, including enterocele (35), rectocele (32), cystocele (18), suprapubic or groin pain (15), and dyspareunia (6). (Demirci F, et al. Long-term results of Burch colposuspension. Gynecol Obstet Invest. 2001;51(4):243–7.)

Laparoscopic Burch procedures have a lower cure rate, higher complication rate, and higher operative cost than open Burch procedures. (Siddighi S, Hardesty JS. Urogynecology & Female Pelvic Reconstructive Surgery. ISBN 0-07-144799-7; Walters, Surgical management of stress incontinence, Clinical Obstetrics & Gynecology-Incontinence. Lipincott William & Wilkins 2004:93–103.) A 2012 Cochrane Review reported that there was insufficient evidence to determine whether the laparoscopic Burch procedure has an advantage over the open Burch procedure in terms of cost-effectiveness, longer-term complications, safety, quality of life, and subjective and objective cure rates. (Lapitan MC, Cody JD. Open retropubic colposuspension for urinary incontinence in women. Cochrane Database Syst Rev. 2012 Jun 13.)

In the SISTEr trial, 47% of the patients undergoing the Burch procedure experienced adverse events. (Albo, ME, et al. Burch Colposuspension versus Fascial Sling to Reduce Urinary Stress Incontinence. N Engl J Med. 2007;356:2143–2155.) Urinary retention rate after Burch is 12%. De novo detrusor overactivity is 16% post-operatively. 25–45% patients with mixed incontinence pre-op will have worse detrusor overactivity post-op. There is a 7–14% risk of enterocele (prolapsed small intestine) formation. 12% have post-colposuspension syndrome, which is chronic pain in the low- to mid-pelvis due to the Burch suture tension. (Siddighi S, Hardesty JS. Urogynecology & Female Pelvic Reconstructive Surgery. ISBN 0-07-144799-7.) Osteitis pubis—which is inflammation of the periosteum from the sutures—occurs at a rate of 2–3%. Dyspareunia increases when combined with vaginal prolapse surgery. Urinary tract

infections and wound complications also occur. (Siddighi S, Hardesty JS. Urogynecology & Female Pelvic Reconstructive Surgery. ISBN 0-07-144799-7.) The Alcalay study reported that 14.7% of the patients had detrusor instability, 22% had long-term voiding difficulty, and 4.6% had recurrent urinary tract infections. The AUA 2012 Update to the SUI Guidelines reported higher rates of pain and sexual dysfunction with the Burch procedure than with midurethral slings. (Guideline for the Surgical Management of Female Stress Urinary Incontinence: 2009 Update Appendices A11 and A16.) The significant post-operative morbidity and complications associated with the Burch procedure has caused surgeons to turn to other procedures to treat SUI. (Wu CJ, et al. The surgical trends and time-frame comparison of primary surgery for stress urinary incontinence, 2006–2010 vs 1997–2005: a population-based nation-wide follow-up descriptive study. Int Urogynecol J. 2014 Dec;25(12):1683–91; Chughtai BI, et al. Midurethral Sling Is the Dominant Procedure For Female Stress Urinary Incontinence: Analysis of Case Logs From Certifying American Urologists. Urology. 2013 Dec;82(6):1267–71; Suskind AM, et al. Effectiveness of Mesh Compared with Nonmesh Sling Surgery in Medicare Beneficiaries. Obstet Gynecol. 2013 Sep;122(3):546–52; Rogo-Gupta L, et al. Trends in the Surgical Management of Stress Urinary Incontinence Among Female Medicare Beneficiaries, 2002–2007. Urology. 2013 Jul;82(1):38–41; Nager CW, et al. A Randomized Trial of Urodynamic Testing before Stress-Incontinence Surgery. N Engl J Med. 2012 May;366(21):1987–97; Wu JM, et al. Trends in inpatient urinary incontinence surgery in the USA, 1998–2007. Int Urogynecol J. 2011 Nov;22(11):1437–43.)

Retropubic needle suspensions have been essentially abandoned due to high failure rates, and they share all of the risks discussed above with respect to retropubic trans-abdominal surgeries.

ii. Bulking Agents

Bulking agents are another option for treatment of SUI. They can be made of bovine collagen or polytetrafluoroethylene (PTFE), and are needle-injected into the urethral submucosa to coapt the urethra. Advantages of these procedures include the fact that they can be office-based, they do not require general anesthesia, they can be performed in patients who are not surgical candidates, and they can be used after failed previous surgeries. While bulking agents are invasive, they are less invasive than other surgical options. Drawbacks of bulking agents include high cost and lower cure rates—25% dry, 50% improved, and 25% requiring repeat injections. Complications include urinary retention (15–25%), urinary tract infection (5–30%), irritative voiding symptoms (less than 20%), allergic reactions (4%), and product migration. (Gross M, et al. Periurethral injections. In: Bent AE, et al., eds. Ostergard's Urogynecology and Pelvic Floor Dysfunction. 5th ed. Lippincott William & Wilkins; 2003:495–502.) "[U]rethral bulking agents are less effective than surgical procedures such as sling placement and are rarely used as primary treatment for stress urinary incontinence." (ACOG / AUGS Practice Bulletin No. 155; Nov. 2015.)

iii. Artificial Urinary Sphincters

Artificial urinary sphincters are inflatable cuffs that surround the proximal urethra and bladder neck. They provide mechanical obstruction of the urethra when inflated and allow

opening with activation of a control pump. Due to the extensive surgery required and long-term complications of device failure (e.g., pump failure, urethral erosion, infection), artificial sphincters are used for severe incontinence when other procedures have failed. (Appell. Techniques and results in the implantation of the artificial urinary sphincter in women with type 3 SUI with vaginal approach. Neurourol Urodyn. 1988;7:613–619.)

iv. Proximal Suburethral Slings

Another surgical treatment option for SUI is the proximal suburethral sling. Originally used only for intrinsic sphincter deficiency ("ISD") and recurrent stress incontinence because of the higher post-operative complications, proximal suburethral slings create a hammock underneath the urethra and bladder neck to prevent descent and provide a backboard for compression of the urethra during increased intra-abdominal pressure. First described in 1907, several biologic and synthetic materials have been used, and bone-anchored slings have also been developed. The biologic materials used include autografts (fascial tissue removed from the patient's abdomen (rectus fascia) or outer thigh (fascia lata)), allografts (sterilized fascia from a cadaver), or xenografts (sterilized fascia from an animal). Modification of the suburethral slings by anchoring to the pubic bone does not increase effectiveness, and carries an increased risk of osteomyelitis. Overall success is between 82–90% at 5 years. Cure rates for SUI with ISD at 5 years is 80–90%, which is higher than Burch. However, in the SISTEr study, 57% of patients receiving a fascial sling had treatment failure at two years' follow-up when all criteria were considered. (Albo, ME, et al. Burch Colposuspension versus Fascial Sling to Reduce Urinary Stress Incontinence. N Engl J Med. 2007;356:2143–2155.) In the extended SISTEr trial, between 2–7 years post-op, continence rates dropped from 52% to 27% in patients who had pubovaginal slings. (Richter HE, et al. Patient Related Factors Associated with Long-Term Urinary Continence After Burch Colposuspension and Pubovaginal Fascial Sling Surgeries. J Urol. 2012 Aug;188(2):485–489.) The 2014 SGS systematic review and meta-analysis by Schimpf, et al. observed that, when comparing pubovaginal slings versus midurethral slings, subjective cure was higher with midurethral slings. Therefore, the authors recommended midurethral slings over pubovaginal slings. (Schimpf MO, et al. Sling surgery for stress urinary incontinence in women: a systematic review and metaanalysis. Am J Obstet Gynecol. 2014;210:1.e1–1.e27.)

Cure rates may be high, but complication rates are also higher with these procedures. These procedures are highly morbid, involve abdominal and transvaginal incisions, greater operative time, more blood loss, and more transfusions; autologous fascia has to be harvested from the patient using a separate incision; recovery time is much longer than other surgical treatment methods; and the complication rate is higher in terms of urinary retention, possible bone anchoring complications, hematoma, chronic pain, infection, exposure, and de novo urinary detrusor overactivity. (Chaikin DC, et al. Pubovaginal fascial sling for all types of stress urinary incontinence: long-term analysis. J Urol. 1998 Oct;160(4):1312–1316; Schimpf MO, et al. Sling surgery for stress urinary incontinence in women: a systematic review and metaanalysis. Am J Obstet Gynecol. 2014;210:1.e1–1.e27; Brubaker L. 5-Year Continence Rates, Satisfaction and Adverse Events of Burch Urethropexy and Fascial Sling Surgery for Urinary Incontinence. Urology. 2012;187:1324–1330; Richter HE, et al. Patient Related Factors Associated with Long-Term Urinary Continence After Burch Colposuspension and Pubovaginal Fascial Sling

Surgeries. Urology. 2012;188:485–489; Albo, ME, et al. Burch Colposuspension versus Fascial Sling to Reduce Urinary Stress Incontinence. N Engl J Med. 2007;356:2143–2155; Rehman H, et al. Traditional suburethral sling operations for urinary incontinence in women. Cochrane Database Syst Rev. 2011 Jan 19;(1):CD001754. doi: 10.1002/14651858.) In the SISTEr trial, 63% of the patients receiving fascial slings experienced adverse events. (Albo, ME, et al. Burch Colposuspension versus Fascial Sling to Reduce Urinary Stress Incontinence. N Engl J Med. 2007;356:2143–2155.) The AUA 2012 Update to the SUI Guidelines reported higher rates of pain and sexual dysfunction with pubovaginal slings than with midurethral slings. (Guideline for the Surgical Management of Female Stress Urinary Incontinence: 2009 Update Appendices A11 and A16.) Harvesting autologous fascia from the abdomen or outer thigh carries a risk of pain, nerve entrapment, and infection, which is a significant drawback to the procedure. The American College of Obstetricians and Gynecologists and the American Urogynecologic Society recommend that autologous fascial bladder neck slings be considered for women who decline or are not candidates for synthetic mesh slings. (ACOG / AUGS Practice Bulletin No. 155; Nov. 2015.) Using allografts and xenografts can be met with cultural or religious objections from patients, and carries a risk of disease transmission and rejection. Allografts and xenografts are also more costly than other materials, and lack the long-term durability of synthetic materials.

v. Midurethral Tension-Free Slings

Midurethral tension-free slings were developed by Ulmsten in Sweden in the 1980s to mid-1990s due to the high morbidity and unpredictable success of retropubic or proximal urethral suspension procedures. These procedures involve the placement of a tension-free synthetic midurethral sling that can be placed either retropubic or transobturator. They act as a hammock or backstop for the midurethra during the moments of increased bladder pressure caused by physical activity. Indications for midurethral slings are SUI with hypermobility of the urethra, SUI with ISD, mixed incontinence with stress predominance, and recurrent SUI following failed previous procedures. They have been used extensively in Europe for the treatment of SUI, became popular in the U.S. in the late 1990s, and have revolutionized the treatment of SUI. (Siddighi S, Hardesty JS. Urogynecology & Female Pelvic Reconstructive Surgery. ISBN 0-07-144799-7.) The majority are performed in ambulatory centers with minimal incision and without the requirement for post-operative catheterization. Other advantages are that it is a shorter learning curve for the surgeon (which means more women have access to the treatment), and they involve less post-operative pain for the patient. Most pelvic floor surgeons prefer synthetic midurethral slings to traditional procedures in most circumstances. (Clemons JL, et al. Impact of the 2011 FDA Transvaginal Mesh Safety Update on AUGS Members' Use of Synthetic Mesh and Biologic Grafts in Pelvic Reconstructive Surgery. Female Pelvic Med Reconstr Surg. 2013;19:191–198; Chughtai BI, et al. Midurethral Sling Is the Dominant Procedure for Female Stress Urinary Incontinence: Analysis of Case Logs From Certifying American Urologists. Urology. 2013 Dec;82(6):1267–71; Nager CW, et al. A Randomized Trial of Urodynamic Testing before Stress-Incontinence Surgery. N Engl J Med. 2012 May 24;366(21):1987–1997.)

IV. Ethicon TVT Products

a. Historical Background of Surgical Use of Mesh

Polypropylene sutures have been used for over 45 years and are biologically compatible with human tissue. Polypropylene hernia mesh has been and continues to be the standard of care for the last thirty years for abdominal wall hernia repair. Polypropylene mesh has been used in open abdominal sacrocolpopexies since the 1960s. The advantage of mesh is augmentation and strength during the healing process with the incorporation of collagen fibers into the material to provide lasting support. I have been performing polypropylene mesh hernia repairs since the 1980s and have never had a patient develop an infection or rejection of the material.

b. The Development of Tension-Free Vaginal Tape Using Prolene Mesh

As mentioned above, midurethral tension-free slings were developed by Ulmsten in Uppsala, Sweden in the 1980s to mid-1990s, at which time he and Dr. Petros experimented with multiple different available materials for the slings, including Mersilene, Marlex, Prolene, Gore-Tex, and others. (Petros PE. Creating a gold standard surgical device: scientific discoveries leading to TVT and beyond: Ulf Ulmsten Memorial Lecture 2014. Int Urogynecol J. 2015 Apr;26(4):471–6; Ulmsten U, et al. A multicenter study of tension-free vaginal tape (TVT) for surgical treatment of stress urinary incontinence. Int Urogynecol J Pelvic Floor Dysfunct. 1998;9(4):210–213; Petros PE, Ulmsten UI. An integral theory and its method for the diagnosis and management of female urinary incontinence. Scand J Urol Nephrol Suppl. 1993;153:1–93.) Dr. Ulmsten and Dr. Petros selected the monofilament, large-pore, knitted, lightweight Prolene mesh due to Prolene's long-term use in surgery as a suture material, its ease of use, and its biocompatibility in the vagina. Dr. Ulmsten also determined that a Prolene sling that was 1 centimeter in width and 40 centimeters in length was optimal. The width of the sling was eventually changed to 1.1 cm, and the length was subsequently increased to 45 cm to facilitate treatment of more women. Dr. Axel Arnaud of Ethicon went to Sweden in 1995 and observed four of Ulmsten's tension-free procedures and negotiated with Ulmsten to purchase the rights to the product he had developed. The TVT has been used extensively in Europe for the treatment of SUI and was introduced to the U.S. in 1998, becoming the gold standard for SUI surgery over the next several years.

c. The TVT, TVT-O, TVT-Exact, and TVT-Abbrevo Devices

The TVT is a monofilament, knitted, macroporous, lightweight, synthetic mesh sling that is swedged onto trocars that are passed at the midurethra via a 1.5 cm vaginal incision under the pubic symphysis and emanating approximately 2 cm lateral from the midline of the abdomen, just above the pubic symphysis. The mesh is encased in a plastic sheath that is removed after deployment of the mesh. The sling is not anchored; it is placed without tension under the mid-urethra, and a cough test is then performed to assess the degree of continence provided by the sling. The ends of the sling are cut beneath the surface of the skin on the abdominal wall after tensioning, and the vaginal incision is closed with an absorbable suture. Cystoscopy is performed to insure the bladder is not perforated by the sling during its deployment. The device comes in a box with the above-mentioned components, along with instructions for use for the

device. Internationally, the TVT is the most common midurethral synthetic sling that is utilized. The TVT has the longest studies available that have demonstrated both low complication rates and high efficacy, with studies carried out as long as 17 years. (Nilsson CG, et al. Seventeen years' follow-up of the tension-free vaginal tape procedure for female stress urinary incontinence. Int Urogynecol J. 2013 Aug;24(8):1265–1269. doi: 10.1007/s00192-013-2090-2.) The TVT is more cost effective, uses less operative time, and has a higher objective cure rate (at less than two years) than the laparoscopic Burch colposuspension. Compared to open Burch procedure, the TVT has a similar cure rate for up to two years of treatment, but is less costly and involves less recovery time. (Siddighi S, Hardesty JS. Urogynecology & Female Pelvic Reconstructive Surgery. ISBN 0-07-144799-7.)

The TVT-O, like the TVT, is a monofilament, knitted, macroporous, synthetic mesh sling that is swedged onto trocars that are passed at the midurethra via a 1.5 cm vaginal incision and through the obturator foramen and out the medial thigh. The same Prolene mesh is used in both the TVT and TVT-O slings. The mesh is a Type I mesh, per the biomaterial classification published by PK Amid in 1997, as it contains pores larger than 75 microns, "which is the required pore size for admission of macrophages, fibroblasts (fibroplasia), blood vessels (angiogenesis) and collagen fibers into the pores." (Amid PK. Classification of biomaterials and their related complications in abdominal wall hernia surgery. Hernia. 1997;1:15–21.) Like the TVT, the mesh of the TVT-O is encased in a plastic sheath that is removed after deployment of the mesh. The sling is not anchored; it is placed without tension, and a cough test is performed to assess the degree of continence provided by the sling. The ends of the sling are cut beneath the surface of the skin on the medial thigh after tensioning, and the vaginal incision is closed with an absorbable suture. It is recommended that cystoscopy be performed following the procedure, but I have found it to be optional due to the decreased likelihood of perforation of the bladder. The device comes in a box with the above-mentioned components along with instructions for use for the device. Hundreds of thousands of TVT-O procedures have been performed internationally since its introduction. It was first introduced in North America in 2004, and I performed the first case in North America in January 2004. The advantage of the transobturator approach is less risk of bladder perforation, retropubic hematoma, and possible bowel injury by avoiding the space of Retzius. The TVT-O procedure has a short learning curve, low morbidity, and a short operating time, and is technically simple to perform, which makes the procedure available to more women. (Groutz A, et al. Long-Term Outcome of Transobturator Tension-Free Vaginal Tape: Efficacy and Risk Factors for Surgical Failure. J Women's Health. 2010;20(10):1525–1528.) There are several long- or intermediate-term studies of the TVT-O supporting its safety and efficacy. (Groutz A, et al. Long-Term Outcome of Transobturator Tension-Free Vaginal Tape: Efficacy and Risk Factors for Surgical Failure. J of Women's Health. 2011;20(10):1525–1528; Laurikainen E, et al. Five-year Results of a Randomized Trial Comparing Retropubic and Transobturator Midurethral Slings for Stress Incontinence. Eur Urol. 2014 Jun;65(6):1109–14; Athanasiou S, et al. Seven years of objective and subjective outcomes of transobturator (TVT-O) vaginal tape: Why do tapes fail? Int Urogynecol J. 2014 Feb;25(2):219–225; Serati M, et al. TVT-O for the Treatment of Pure Urodynamic Stress Incontinence: Efficacy, Adverse Effects, and Prognostic Factors at 5-Year Follow-up. Eur Urol. 2013;63:872–78; Liapis A, et al. Efficacy of inside-out transobturator vaginal tape (TVTO) at 4 years follow up. Eur J Obstet Gynecol Reprod Biol. 2010 Feb;148(2):199–201; Angioli R, et al. Tension-Free Vaginal Tape Versus Transobturator Suburethral Tape: Five-Year Follow-up

Results of a Prospective, Randomised Trial. Eur Urol. 2010;58:671–677; Cheng D, et al. Tension-free vaginal tape-obturator in the treatment of stress urinary incontinence: a prospective study with five-year follow-up. Eur J Obstet Gynecol Reprod Biol. 2012;161:228–231.)

The TVT-Exact Continence System is a retropubic midurethral sling consisting of laser-cut Prolene polypropylene mesh that is 1.1 cm x 45 cm, covered by a clear plastic Implant Sheath and held between two white Trocar Sheaths that are bonded to the TVT-Exact implant and Implant Sheath. The mesh used in the TVT-Exact is the same lightweight, macroporous, monofilament mesh used in the TVT and TVT-O devices. The trocars of the TVT-Exact are thinner (3 mm v. 5 mm) and longer than the trocars of the TVT device. The device was launched in 2010. Thubert and colleagues published a retrospective study of 98 patients receiving either TVT or TVT-Exact who were followed for a minimum of one year. The authors found no significant difference in the rate of bladder injury. They also found less intense immediate post-operative pain in the TVT-Exact cohort, but by six weeks after surgery, the prevalence of pain ≥ 20/100 (VAS) no longer differed between the two groups. There was an increased post-void residual in the TVT-Exact group, but there was no between-group difference in post-operative self-catheterization, and the rate of tape release or cutting was also comparable in the two groups. The authors found a higher rate of post-operative bladder outlet obstruction symptoms in the TVT-Exact group, but there was no difference between the two groups when considering only de novo bladder outlet obstruction. The study showed that the prevalence of peri- and post-operative complications was equal in the two groups, and there was no significant difference in the success rate (no reported SUI and negative cough stress test). (Thubert T, et al. Bladder injury and success rates following retropubic mid-urethral sling: TVT EXACT vs. TVT. Eur J Obstet Gynecol Reprod Biol. 2016 Mar;198:78–83.)

The TVT-Abbrevo, like the TVT-O, is a transobturator midurethral sling consisting of laser-cut Prolene polypropylene mesh that is 1.1 cm x 12 cm, covered by clear polyethylene sheaths, and held between two Helical Passer Sheaths that are bonded to the mesh implant sheaths and the device's Positioning Lines, which are made of Prolene polypropylene monofilament suture. The device was developed by Professor Jean de Leval and Dr. David Waltregny. The mesh used in the TVT-Abbrevo is the same lightweight, macroporous, monofilament mesh used in the TVT and TVT-O devices. The device also comes with an Atraumatic Winged Guide, which is a stainless steel accessory that facilitates consistent passage of the TVT-Abbrevo implant through the dissection tract. It has a placement loop that aids the surgeon in centering the device. The device is implanted in a procedure involving reduced paraurethral dissection than the TVT-O procedure, with the obturator membrane being perforated only by the helical passer. The product was launched in 2010. There are several studies of the TVT-Abbrevo supporting its safety and efficacy and showing equal efficacy to the TVT-O, with low/equivalent complication rates and, in general, less pain in the early post-operative period.

In 2011, Dr. Piet Hinoul and colleagues published a cadaver study on an anatomic comparison of the TVT-O and a modified TVT-O that had only 12 cm of mesh (like the TVT-Abbrevo) rather than 45 cm, and found the modified device traversed fewer muscular structures, passed farther away from the obturator canal, the anterior obturator nerve, and the posterior obturator nerve, but the differences were not statistically significant. The modified device resulted in the implantation of significantly less mesh, while still consistently anchoring in the

obturator membrane. (Hinoul P, et al. An anatomic comparison of the original versus a modified inside-out transobturator procedure. Int Urogynecol J. 2011;22:997–1004.) Drs. Jean de Leval, Alexandre Thomas, and David Waltregny, also in 2011, published the one-year results of a prospective randomized controlled trial involving the TVT-O device and the same modified TVT-O device used in the aforementioned anatomic cadaver study. They studied 175 patients randomized to either the TVT-O (n=87) or modified TVT-O (n=88). There was no statistically significant difference in cure rates between the two groups (91.7% TVT-O and 90.7% modified TVT-O), but they found an increase in the incidence and intensity of groin pain in the original TVT-O group on day 0 and 1, but not thereafter. One patient receiving a TVT-O had a suburethral vaginal exposure requiring partial tape excision, but there were no exposures in the modified TVT-O group. (de Leval J, et al. The original versus a modified inside-out transobturator procedure: 1-year results of a prospective randomized trial. Int Urogynecol J. 2011;22:145–56.)

Drs. Waltregny and de Leval published three-year data on their randomized controlled trial involving the TVT-O versus TVT-Abbrevo in 2012. 87% of the patients completed the 3-year follow-up, and an 84.3% subjective cure rate was seen overall, with no statistically significant difference between the two groups. 85.7% of the TVT-O patients and 87.7% of the TVT-Abbrevo patients had a negative cough test at the 3-year follow-up ($p>0.05$). 1 patient (1.3%) in the TVT-O group and 3 patients (4.1%) in the TVT-Abbrevo group reported thigh pain at three years, but did not complain about the pain and had a pain score of ≤ 3. (Waltregny D, de Leval J. New Surgical Technique for Treatment of Stress Urinary Incontinence—TVT-ABBREVO: From Development to Clinical Experience. Surg Technol Int. 2012 Dec;22:149–57.) Dr. Giovanni A. Tommaselli and colleagues published their single-blind randomized study of the TVT-O and TVT-Abbrevo in 2012. They studied 72 patients randomized to either the TVT-O procedure or the TVT-Abbrevo procedure and evaluated post-operative pain, objective cure rate, and quality-of-life scores. They found that pain scores were significantly lower in the TVT-Abbrevo group at 24 hours after the surgery, but they did not find any significant difference in the number of analgesic vials administered, cure rates, and questionnaire scores between the two groups. At one month after surgery, there was no significant difference between the VAS pain scores in the groups. (Tommaselli GA, et al. Effects of a modified technique for TVT-O positioning on postoperative pain: single-blind randomized study. Int Urogynecol J. 2012;23:1293–99.) Dati and colleagues conducted a randomized controlled trial involving patients treated with TVT-Abbrevo or the Ajust Mini-Sling, and found higher cure rates in the TVT-Abbrevo patients. (Dati S, et al. Single-Incision Minisling (Ajust) vs. Obturator Tension-Free Vaginal Shortened Tape (TVT_Abbrevo) in Surgical Management of Female Stress Urinary Incontinence. Int J Gynecol & Obstet. 2012;119S3:S531–S867, Abs. M432.)

Narang and colleagues conducted a study of 56 patients who were treated with the TVT-Abbrevo. The authors found that at one month, 98% of patients were subjectively cured of SUI, and that 89.3% were subjectively cured at 6 months. Objective cure based on urodynamic testing was 88.8% at 6 months. At 1 month, 1 patient had pain, and the mean pain score was 0.04 ± 0.28. At 6 months and 1 year, no patients had pain. There was one patient who developed a tape erosion in the vagina at 6 months, and 1 patient who developed recurrent UTIs over 6 months. (Narang S, Han HC. Initial Experience of TVT-Abbrevo at a Tertiary Care Hospital. ICS Abs. 682, 2013.) In 2014, Capobianco and colleagues published the results of a

study of 56 women treated with the TVT-Abbrevo with 2-year follow-up. The authors found that 76.79% of patients were subjectively cured at 1 year, with an additional 17.86% of patients experiencing considerable improvement in symptoms. There was only 1 case of de novo OAB. There were no cases of vaginal erosion at follow-up visit, and no cases of persistent groin pain at long-term follow-up. The authors concluded that the TVT-Abbrevo provides "high objective and subjective long term efficacy, a clinically meaningful improvement in patient quality of life, and an excellent safety profile." They found the positioning of the TVT-Abbrevo to be technically simple, and found it very easy to position the tape lying flat under the urethra. (Capobianco G, et al. TVT-ABBREVO: efficacy and two years follow-up for the treatment of stress urinary incontinence. Clin Exp Obstet Gynecol. 2014;41(4):445–7.)

In 2014, Kurien and colleagues reported on a prospective cohort study of the efficacy and safety of the TVT-Abbrevo with a maximum of 22-month follow-up and found a subjective cure rate of 94.6% at 1 year and an objective cure rate of 86.7% at 6 months. Seventy-nine percent of the patients were relieved of their urgency and urge incontinence, and 8.3% had an improvement of their OAB symptoms at one year. There were no bladder perforations and only 2 vaginal perforations. Only 7 of the 76 patients had any pain at the first follow-up on day 3–10, but none of the 7 had a VAS score of greater than 5. Persistent pain needing any kind of analgesia was 0% at 1 month, 6 months, and 1 year. Only 2 of the 76 patients experienced a vaginal tape erosion, and they were asymptomatic. There were no recurrent urinary tract infections at one year, and de novo OAB symptoms were noted in only 1 patient at 1-year follow-up. (Kurien A, et al. TVT Abbrevo for management of female stress urinary incontinence: a prospective analysis over 22 months in a tertiary care hospital. Br J Obstet Gynecol. 2014 Jan;121(2):235–236 EP13.17.) In 2015, Shaw and colleagues reported the results of their retrospective cohort study of all women undergoing treatment with a TVT-O or a TVT-Abbrevo. The authors found that only 1 patient in the TVT-Abbrevo group experienced bothersome groin pain, and concluded that use of the TVT-Abbrevo reduces post-operative groin pain compared to the TVT-O without any reduction in efficacy. (Shaw JS, et al. Decreasing transobturator sling groin pain without decreasing efficacy using TVT-Abbrevo. Int Urogynecol J. 2015 Sep;26(9):1369–72.)

Canel and colleagues published a retrospective study comparing 50 patients treated with the TVT-Abbrevo to 50 patients treated with the TVT-O. They found there to be less post-operative pain in the TVT-Abbrevo group than in the TVT-O group, but at 6 weeks after surgery, there was no statistically significant difference between the two groups of patients. There was no statistically significant difference in the rate of de novo bladder outlet obstruction symptoms, and the rate of peri- and post-operative complications were equal in the two groups. Success rates between the groups were also similar at 12 months after surgery. (Canel V, et al. Postoperative groin pain and success rates following transobturator midurethral sling placement: TVT ABBREVO® system versus TVT™ obturator system. Int Urogynecol J. 2015 Oct;26(1):1509–16.)

In 2016, Tommaselli and colleagues published a retrospective study looking at cure rates and complications in overweight and normal-weight women undergoing the TVT-Abbrevo procedure. The authors found no statistically significant difference in objective or subjective cure rates at 12-month follow-up. There were no serious intra-operative or post-operative complications observed, and there were no differences in pain visual analogue scores or the

number of analgesic vials administered in the two groups of women. (Tommaselli GA, et al. Efficacy and safety of the trans-obturator TVT-Abbrevo device in normal weight compared to overweight patients affected by stress urinary incontinence. Eur J Obstet Gynecol Reprod Biol. 2016 Feb;197:116–9.)

A recent high-quality Cochrane meta-analysis review of the literature concludes that midurethral slings like the TVT, TVT-O, TVT-Abbrevo, and TVT-Exact have similar efficacy to the Burch procedure, but the midurethral sling procedures involve shorter recovery time. The review further concludes that midurethral synthetic sling operations are the most extensively researched surgical treatment for SUI in women and have a good safety profile. The TVT, in particular, is the most studied mesh device, with more than 100 randomized controlled trials having been done with the device. The mesh used in the TVT, TVT-O, TVT-Abbrevo, and TVT-Exact is the most studied of any of the meshes used in stress incontinence surgery. The Cochrane review authors note that irrespective of the routes traversed, synthetic mesh midurethral slings are highly effective in the short- and medium-term, and evidence demonstrates their effectiveness in the long-term. The Cochrane Review illustrates positive impact on improving the quality of life of women with SUI. With the exception of groin pain, fewer adverse events occur with employment of a transobturator approach. (Ford AA, Rogerson L, Cody JD, Ogah J. Mid-urethral sling operations for stress urinary incontinence in women. Cochrane Database Syst Rev. 2015, Issue 7. Art. No.: CD006375. doi: 10.1002/ 14651858.CD006375.pub3.) The 2015 Cochrane systematic review demonstrates that both retropubic and transobturator approaches appear to be comparable in terms of efficacy and patient satisfaction. (ACOG / AUGS Practice Bulletin No. 155; Nov. 2015.) However, a 2015 systematic review and meta-analysis observed similar rates of objective cure between transobturator and retropubic midurethral slings, and higher subjective cure rates in retropubic slings. (Tommaselli GA, et al. Medium-term and long-term outcomes following placement of midurethral slings for stress urinary incontinence: a systematic review and metaanalysis. Int Urogynecol J. 2015 Sep;26(9):1253–68. doi: 10.1007/s00192-015-2645-5.)

In 2010, Novara added 14 new trials to their 2007 systematic review metaanalysis evaluating efficacy, complication rate, and reoperation rate of Burch colposuspension and synthetic midurethral slings. Midurethral slings were found to have higher objective cure rates than Burch colposuspension. Similar rates of postoperative complications, including pelvic hematoma, UTI, postoperative lower urinary tract symptoms, and reoperation were noted between the two groups. Midurethral slings resulted in a greater improvement in patient quality of life over the Burch procedure in two trials. Midurethral slings were also found to be more cost-effective than the Burch procedure. (Cox A, Herschorn S, Lee L. Surgical management of female SUI: is there a gold standard? Nat Rev Urol. 2013 Feb;10(2):78–89. doi: 10.1038/ nrurol.2012.243. Erratum: Nat Rev Urol. 2013 Apr;10(4):188.) Based on the literature, a new gold standard for first-line surgical treatment for women with SUI has emerged—the synthetic midurethral sling inserted via retropubic or transobturator approach. (Cox A, Herschorn S, Lee L. Surgical management of female SUI: is there a gold standard? Nat Rev Urol. 2013 Feb;10(2):78–89. doi: 10.1038/nrurol.2012.243. Erratum: Nat Rev Urol. 2013 Apr;10(4):188.) Studies have shown that midurethral slings are superior to both the Burch procedure and pubovaginal slings in terms of cure rates. (Schimpf MO, et al. Sling surgery for stress urinary incontinence in women: a systematic review and metaanalysis. Am J Obstet Gynecol.

2014;210:1.e1–1.e27.) Objective cure rate at one year is greater than 90%, and 85% at seventeen years. (Nilsson CG, et al. Seventeen years' follow-up of the tension-free vaginal tape procedure for female stress urinary incontinence. Int Urogynecol J. 2013 Aug;24(8):1265–1269. doi: 10.1007/s00192-013-2090-2.)

Due to the increased morbidity of the open Burch procedure, it is less frequently taught in residencies and fellowships. Almost all residents, however, are trained on midurethral slings as the primary treatment option for SUI management. The TVT retropubic and transobturator approaches are commonly taught and performed in training programs throughout the world.

The TVT and TVT-O have proven long-term efficacy due to the permanence and stability of the mesh and are superior in efficacy to retropubic suspensions. (Aigmueller T, et al. Ten-year follow-up after the tension-free vaginal tape procedure. Am J Obstet Gynecol. 2011 Nov;205(5):496.e1–5.) Compared with open or laparoscopic colposuspension the success rates are more stable with a lesser decline of success over years. Reported long-term success rates after open or laparoscopic colposuspension vary between 36% and 69%. (Alcalay M, et al. Burch colposuspension: a 10–20 year follow up. Br J Obstet Gynaecol. 1995;102:740–745; Barr S. The long-term outcome of laparoscopic colposuspension: a 10-year cohort study. Int Urogynecol J Pelvic Floor Dysfunct. 2009 Apr:20(4):443–5. doi: 10.1007/s00192-008-0798-1.)

I have personally performed over 1,000 TVT procedures, including the TVT, the TVT-O and the more recent TVT-Exact and TVT-Abbrevo, and have found the products to be safe and efficacious when following the appropriate patient selection and the technique described by Drs. Ulmsten and de Leval, which is covered in the product instructions for use. I have lectured and proctored physicians on the safe use of the TVT, TVT-O, and several other devices since 2000. The devices are high quality, straightforward, and the polypropylene mesh is stable over time, as I have patients implanted 15 years ago and see no long-term complication trends. Since the television advertisements claiming pelvic mesh is a dangerous product, I have received hundreds of phone calls from anxious patients with fears of product recalls and future complications. The overwhelming majority of those anxious patients have excellent outcomes and no adverse symptoms. The effect on current patients is to create fear that a synthetic sling will cause future problems and many choose not to proceed to treatment. There is a 30% reduction in the number of patients undergoing stress incontinence and pelvic reconstructive surgery. (Perkins CE, Warrior K, Eilber KS, et al. The Role of Mid-urethral Slings in 2014: Analysis of the Impact of Litigation on Practice. Curr Bladder Dysfunct Rep. (2015) 10:39–45. doi: 10.1007/s11884-014-0278-z; Koo K, Gormley EA. Abstract MP81-05: Transvaginal Mesh in the Media Following the 2011 FDA Update.)

The efficacy and safety of the TVT-O, TVT-Abbrevo, and the retropubic TVT slings are well-reported. The TVT is the most studied midurethral sling, with more than 100 RCTs. The TVT-O has also been extensively studied—with thousands of patients included in the collection of studies. Additionally, the following professional organization position statements and guidelines and FDA publications have addressed the safety, efficacy, and widespread acceptance of synthetic mesh midurethral slings like the TVT and TVT-O.

- **ACOG / AUGS Practice Bulletin No. 155 (Nov. 2015)**
  - "Synthetic midurethral mesh slings are the most common primary surgical treatment for stress urinary incontinence in women. Synthetic midurethral slings demonstrate efficacy that is similar to traditional suburethral fascial slings, open colposuspension, and laparoscopic colposuspension. Compared with suburethral fascial slings, fewer adverse events have been reported with synthetic midurethral slings. Voiding dysfunction is more common with open colposuspension than with synthetic midurethral slings. For these reasons, midurethral synthetic mesh slings have become the primary surgical treatment for stress urinary incontinence in women."
  - "Although controversy exists about the role of synthetic mesh used in the vaginal repair of pelvic organ prolapse, there are substantial safety and efficacy data that support the role of synthetic mesh midurethral slings as a primary surgical treatment option for stress urinary incontinence in women. For this reason, and to clarify uncertainty for patients and practitioners, the American Urogynecologic Society and the Society of Urodynamics, Female Pelvic Medicine & Urogenital Reconstruction published a position statement recognizing polypropylene mesh midurethral slings as the 'standard of care' in the surgical treatment of stress urinary incontinence."
- **AUGS-SUFU, Position Statement on Mesh Midurethral Slings for Stress Urinary Incontinence (Jan. 3, 2014) (updated June 2016 and supported by the American Association of Gynecological Laparoscopists, the American College of Obstetricians and Gynecologists, the National Association for Continence, the Society of Gynecologic Surgeons, and the Women's Health Foundation)**
  - "Polypropylene material is safe and effective as a surgical implant. Polypropylene has been used in most surgical specialties (including general surgery, cardiovascular surgery, transplant surgery, ophthalmology, otolaryngology, gynecology, and urology) for over five decades, in millions of patients in the US and the world (personal communication with manufacturers of polypropylene suture and mesh)."
  - "As a knitted implant for the surgical treatment of SUI, macroporous, monofilament, light weight polypropylene has demonstrated long term durability, safety, and efficacy up to 17 years."
  - "The monofilament polypropylene mesh MUS is the most extensively studied anti-incontinence procedure in history. A broad evidence base including high quality scientific papers in medical journals in the US and the world supports the use of the MUS as a treatment for SUI. There are greater than 2000 publications in the scientific literature describing the MUS in the treatment of SUI. These studies include the highest level of scientific evidence in the peer reviewed scientific literature. . . . No other surgical treatment for SUI before or since has been subject to such extensive investigation."
  - "Polypropylene mesh midurethral slings are the standard of care for the surgical treatment of SUI and represent a great advance in the treatment of

this condition for our patients. Since the publication of numerous level one randomized comparative trials, the MUS has become the most common surgical procedure for the treatment of SUI in the US and the developed world. This procedure has essentially replaced open and transvaginal suspension surgeries for uncomplicated SUI. . . . Full-length midurethral slings, both retropubic and transobturator, have been extensively studied, are safe and effective relative to other treatment options and remain the leading treatment option and current gold standard for stress incontinence surgery. Over 3 million MUS have been placed worldwide and a recent survey indicates that these procedures are used by > 99% of AUGS members."

- "The polypropylene midurethral sling has helped millions of women with SUI regain control of their lives by undergoing a simple outpatient procedure that allows them to return to daily life very quickly. With its acknowledged safety and efficacy it has created an environment for a much larger number of women to have access to treatment. In the past, concerns over failure and invasiveness of surgery caused a substantial percent of incontinent women to live without treatment. One of the unintended consequences of this polypropylene mesh controversy has been to keep women from receiving any treatment for SUI. This procedure is probably the most important advancement in the treatment of stress urinary incontinence in the last 50 years and has the full support of our organizations which are dedicated to improving the lives of women with urinary incontinence."

- **AUGS Position Statement on Restriction of Surgical Options for Pelvic Floor Disorders (2013)**
  - "The American Urogynecologic Society strongly opposes any restrictions by state or local medical organizations, healthcare systems, or insurance companies which ban currently available surgical options performed by qualified and credentialed surgeons on appropriately informed patients with pelvic floor disorders."
  - "In a recent study involving 53 expert urologists and urogynecologists (of whom > 90% were fellowship trained) and who could select among many surgical options, the full-length synthetic midurethral sling was the preferred option in 93% for the surgical treatment of primary stress incontinence. Full-length midurethral slings, both retropubic and transobturator, have been extensively studied, are safe and effective relative to other treatment options and remain the leading treatment option and current gold standard of care for stress incontinence surgery."
- **AUA Position Statement on the Use of Vaginal Mesh for the Surgical Treatment of Stress Urinary Incontinence (Nov. 2011)**
  - "Suburethral synthetic polypropylene mesh sling placement is the most common surgery currently performed for SUI. Extensive data exist to support the use of synthetic polypropylene mesh suburethral slings for the treatment of female SUI, with minimal morbidity compared with alternative surgeries. Advantages include shorter operative

time/anesthetic need, reduced surgical pain, reduced hospitalization, and reduced voiding dysfunction. Mesh-related complications can occur following polypropylene sling placement, but the rate of these complications is acceptably low."

- "Multiple case series and randomized controlled trials attest to the efficacy of synthetic polypropylene mesh slings at 5–10 years. This efficacy is equivalent or superior to other surgical techniques. There is no significant increase in adverse events observed over this period of follow-up. Based on these data, the AUA Guideline for the Surgical Management of Stress Urinary Incontinence (2009) concluded that synthetic slings are an appropriate treatment choice for women with stress incontinence, with similar efficacy but less morbidity than conventional non-mesh sling techniques."

- **IUGA – Stress Urinary Incontinence – A Guide for Women (2011)**
  - "Before 1993, the treatment of stress incontinence often involved major surgery with an abdominal incision. The most common treatment now involves the use of a permanent sling that lies under the middle section of the urethra."
- **ICS Fact Sheets: A Background to Urinary and Faecal Incontinence (July 2013)**
  - "Worldwide, midurethral slings comprised of synthetic mesh have become the treatment of choice for SUI. Long-term data are robust and demonstrate durable efficacy with a very low complication rate, particularly in experienced hands. Various techniques for sling placement and different meshes are employed according to physician preference, but all appear to be equally effective."
- **Lucas MG, Ruud JLB, Burkhard FC, et al. EAU Guidelines on Surgical Treatment of Urinary Incontinence. Eur Urol. 2012 Dec;62(6):1118–1129.**
  - "There has been a rapid adoption of midurethral synthetic sling insertion as the first-line surgical option for SUI because it is effective, it is less invasive, and patients recover more quickly."
  - Notes that a systematic review of midurethral slings with both open colposuspension and laparoscopic colposuspension showed that retropubic insertion of a synthetic midurethral sling gave equivalent patient-reported and superior clinician-reported cure of SUI compared with colposuspension at 12 months; transobturator insertion gave equivalent patient-reported and clinician-reported cure of SUI at 12 months. Also notes that midurethral sling insertion was associated with a lower rate of new symptoms of urgency and voiding dysfunction compared with colposuspension.
- **NICE clinical guideline 171. Urinary incontinence: The management of urinary incontinence in women. (Sept. 2013)**
  - Notes that if conservative management for SUI has failed, the surgeon should offer, among other options, a synthetic midurethral tape.
  - Notes that, when offering a synthetic midurethral tape procedure, surgeons should use procedures and devices for which there is current high quality

evidence of efficacy and safety. Footnote 11 then notes that at the time of publication, TVT and TVT-O (among others) met this guideline.

- **FDA, Considerations about Surgical Mesh for SUI (2013)**
  - "Mesh sling procedures are currently the most common type of surgery performed to correct SUI. Based on industry estimates, there were approximately 250,000 of these procedures performed in 2010."
  - "The safety and effectiveness of multi-incision slings is well-established in clinical trials that followed patients for up to one-year. Longer follow-up data is available in the literature, but there are fewer of these long-term studies compared to studies with one-year follow-up."
- **FDA Executive Summary, Surgical Mesh for Treatment of Women with Pelvic Organ Prolapse and Stress Urinary Incontinence (Sept. 8–9, 2011)**
  - Notes that the Burch has a long history, but its popularity has declined over the past two decades with the introduction of less invasive procedures. Notes that pubovaginal sling procedures using biologic graft material (often autologous fascia) similarly have declined in popularity.
  - Notes that anterior repair with Kelly plication to correct SUI in the presence of a cystocele and bladder neck needle suspension is rarely performed currently due to poor long-term outcomes.
  - "A substantial number of quality clinical trials, as well as systematic reviews, have been published for the first generation minimally invasive slings that provide evidence of safety and effectiveness of these devices." (p. 28).
  - "After considering all available data on both safety and effectiveness, and considering the risk/benefit profile, it appears that new premarket clinical trials are not warranted for minimally invasive slings for SUI unless the device has new features (*e.g.* new polymer or coating) that could affect device performance."
- **FDA 24-hr Summary – Ob/Gyn Devices Panel (Sept. 8–9, 2011)**
  - Notes that the panel consensus on retropubic and transobturator suburethral slings was that the "safety and effectiveness of these devices is well-established."
- **Dmochowski RR, Blaivas JM, Gormley EA, et al. Update of AUA Guideline on the Surgical Management of Female Stress Urinary Incontinence. J Urol. 2010 May;183(5):1906–1914.**
  - Noting the importance of the transobturator technique in the treatment of SUI and that midurethral slings are one treatment modality that may be considered for the index patient.
- **AUA Position Statement on the Use of Vaginal Mesh for the Surgical Treatment of Stress Urinary Incontinence (2012)**
  - "Suburethral synthetic polypropylene mesh sling placement is the most common surgery currently performed for SUI. Extensive data exist to support the use of synthetic polypropylene mesh suburethral slings for the treatment of female SUI, with minimal morbidity compared with alternative surgeries. Advantages include shorter operative time/anesthetic need, reduced surgical pain, reduced hospitalization, and

reduced voiding dysfunction. Mesh-related complications can occur following polypropylene sling placement, but the rate of these complications is acceptably low. Furthermore, it is important to recognize that many sling-related complications are not unique to mesh surgeries and are known to occur with non-mesh sling procedures as well. It is the AUA's opinion that any restriction of the use of synthetic polypropylene mesh suburethral slings would be a disservice to women who choose surgical correction of SUI."

- "Multiple case series and randomized controlled trials attest to the efficacy of synthetic polypropylene mesh slings at 5–10 years. This efficacy is equivalent or superior to other surgical techniques. There is no significant increase in adverse events observed over this period of follow-up. Based on these data, the AUA Guideline for the Surgical Management of Stress Urinary Incontinence (2009) concluded that synthetic slings are an appropriate treatment choice for women with stress incontinence, with similar efficacy but less morbidity than conventional non-mesh sling techniques."

Plaintiffs' experts' theory of mesh degradation is not substantiated in the literature or in my personal experience using polypropylene slings and mesh for incontinence treatment and pelvic reconstruction. Studies of explanted mesh are difficult to interpret, as there is damage to the material during explantation, treatment with chemicals to remove the collagen and biologic matrix that has incorporated into the mesh, and preparation onto slides for microscopic examination. There is no literature to support clinically significant mesh degradation in humans. Polypropylene suture is used by vascular surgeons on major blood vessels, and in my practice, when tying off renal arteries and repairing the largest vein in the body; the vena cava. If there was a question of degradation or loss of strength over time, Prolene suture would not be the suture of choice for the highest-risk surgery. The studies often relied on by plaintiffs' experts, offering the opinion that the Prolene mesh degrades, are unreliable and do not support that theory. For instance, the Clavé study from 2010 is unreliable and does not show degradation. The chemical analyses performed on a limited subset of the specimens does not show degradation, and the scanning electron microscope photos in the study show surface cracking that could be from biologic material and handling or preservation rather than the cracking of the polypropylene itself. Also, the sample analyzed in the study was only 32 out of the 100 specimens, and the authors fail to discuss how those 32 specimens were selected. They also fail to discuss whether the mesh was damaged during surgical explantation. Other literature indicates that cracking seen on the surface of explanted Prolene or polypropylene is not degraded Prolene or polypropylene, but rather a cracked biofilm. (de Tayrac R and Letouzey V, Basic science and clinical aspects of mesh infection in pelvic floor reconstructive surgery, Int Urogynecol J. 2011 Jul;22(7):775-80; Ong KL, White J, and Thames SF, The Myth: In Vivo Degradation of Polypropylene Meshes, IUGA Abs. PP 19, 2016.)

Nor have I seen a problem with Prolene mesh roping or curling, unless it is placed improperly by over-tensioning. Nor have I observed particle loss from mechanically cut mesh in my practice. Even if there were particle loss from the mechanically cut Prolene mesh, the particles lost would be the same Prolene as the suture material that is FDA approved as safe and

effective for use in the human body. Furthermore, the mesh does not contract or experience pore collapse when placed according to the IFU. The sheath that covers the mesh on the TVT, TVT-O, TVT-Abbrevo, and TVT-Exact devices protects the tissue against trauma, helps the mesh pass through the tissue smoothly, and carries the forces of implantation so that the mesh retains its shape. Scar tissue that forms after any pelvic surgery contracts, and tissue incorporating into implanted mesh is no exception, but the mesh itself does not contract. (Nilsson, CG. Seventeen years' follow-up of the tension-free vaginal tape procedure for female stress urinary incontinence. Int Urogynecol J. 2013 Aug;24(8):1265–1269; Lukacz ES, et al. The effects of the tension-free vaginal tape on proximal urethral position: a prospective, longitudinal evaluation. Int Urogynecol J Pelvic Floor Dysfunct. 2004 Jan–Feb;15(1):32–38; discussion 38.)

There is no practical or clinical difference between mechanically cut or laser-cut mesh in terms of how it is deployed or incorporated in the tissues. (ETH.MESH.01784823–28 (CER Laser Cut Mesh); ETH.MESH.01222075–79 (Elongation Characteristics of Laser Cut Prolene Mesh for TVT); ETH.MESH.06696367–79 (Performance Evaluation of TVT U Prolene Mesh); Lin AT, et al. In Vivo tension Sustained by Fascial Sling in Pubovaginal Sling Surgery for Female Stress Urinary Incontinence. J Urol. 2005 Mar;173(3):894–897.) Mesh is not pre-stretched to 50% elongation before it is used, and it is implanted with trocars and with a protective sheath over the mesh. The mesh sling must be stiff enough to lie flat against the posterior urethra with porosity large enough to encourage fibroblast and collagen deposition for incorporation, and it must have enough elasticity to allow give during dynamic stressing that occurs with activity. Mesh requires an optimal level of stiffness to properly do its job supporting the urethra. Based on my experience and my assessment of the available literature, I do not believe that any particle loss from mechanically cut Prolene polypropylene mesh has a clinical effect in patients. Both laser-cut and mechanically cut Prolene mesh is safe and efficacious as demonstrated by the medical literature and in my experience.

Plaintiffs' experts assert that the Prolene mesh used in the TVT, TVT-O, TVT-Abbrevo, and TVT-Exact devices is small-pore mesh. That is not true. The Ethicon TVT mesh has the largest porosity, and greatest elasticity of all the SUI meshes available. It is also monofilament and knitted to provide the optimal combination of biocompatibility and minimal inflammatory response. The mesh—which has a pore size of approximately 1,379 microns—allows adequate tissue incorporation/ingrowth. (Amid PK. Classification of biomaterials and their related complications in abdominal wall hernia surgery. Hernia. 1997;1(1):15–21.) The Ethicon mesh is not associated with an increased risk of infection compared to other SUI vaginal surgeries. Verified infection after TVT, TVT-O, TVT-Abbrevo, or TVT-Exact is a very rare occurrence, and has not occurred in my practice in over 1,000 cases and 15 years.

Nor is the mesh in the TVT, TVT-O, TVT-Abbrevo, or TVT-Exact devices "heavyweight" mesh. Synthetic slings require an optimal amount of weight/density to properly do their job supporting the urethra without adversely affecting its function. Indeed, seventeen-year follow-up substantiates the biocompatibility of the weight/stiffness/elasticity and porosity of the TVT mesh. At seventeen years of follow-up, 91.3% of patients' SUI was objectively cured, and there was no tape rejection, no clinically significant contracture, and only one mesh exposure, which was not symptomatic and was due to vaginal atrophy in an elderly patient.

(Nilsson, CG. Seventeen years' follow-up of the tension-free vaginal tape procedure for female stress urinary incontinence. Int Urogynecol J. 2013 Aug;24(8):1265–1269.)

Plaintiffs' experts have also claimed that the mesh used in the TVT, TVT-O, TVT-Abbrevo, and TVT-Exact devices is cytotoxic and causes an excessive inflammatory response. This is not supported in the literature, and I have not seen it in my practice. The long-term studies on the TVT and TVT-O mesh belie this claim. Studies show minimal inflammation associated with the Prolene mesh used in TVT and TVT-O, and practically no tissue reaction out to two years. (Falconer C, et al. Influence of different sling materials on connective tissue metabolism in stress urinary incontinent women. Int Urogynecol J Pelvic Floor Dysfunct. 2001;12 Suppl 2:S19–23.) The mere presence of chronic inflammatory cells in a tissue specimen does not prove that there is a chronic inflammatory process that is active. Such cells can be present but quiescent, and can be seen in vaginal tissue even when no mesh or other foreign body has been implanted. If it were the case that the mesh in the TVT, TVT-O, TVT-Abbrevo, and TVT-Exact devices was cytotoxic, the many intermediate- and long-term studies on the TVT and TVT-O devices would not demonstrate the high efficacy and low complication rates that they do.

Any suggestion by plaintiffs' experts that PVDF is a safer alternative to the Prolene mesh used in the TVT, TVT-O, TVT-Abbrevo, and TVT-Exact devices is untenable. There is no mid- or long-term data supporting the use of PVDF in SUI treatment. To my knowledge, PVDF has not been studied to treat SUI in women. Plaintiffs' experts may also claim that Ultrapro or Vypro mesh would have been a safer alternative to the Prolene mesh used in the TVT and TVT-O slings. However, with respect to Vypro, a study of the use of that mesh in pelvic floor surgery showed that tolerance of the Vypro mesh was "very poor" and associated with high rates of erosion and cicatrisation. (Denis S, et al. Pelvic Organ Prolapse Treatment by the Vaginal Route Using a Vypro Composite Mesh: Preliminary Results About 106 Cases. ICS IUGA 2004; Abstract 620.) With respect to Ultrapro, the study often cited by plaintiffs' experts in support of that material as a safer alternative to the Prolene TVT mesh is the Okulu study, but that study does not compare TVT mesh to Ultrapro mesh, and involves a technique completely different than the one used to implant the TVT or TVT-O slings. (Okulu E, et al. Use of three types of synthetic mesh material in sling surgery: A prospective randomized clinical trial evaluating effectiveness and complications. Scand J Urol. 2013 Jun;47(3):217–224.) Ethicon studied the use of Ultrapro mesh with a sheath and found that the force required to remove the sheath was excessive, which it believed to be due to the fact that the mesh stuck to the sheath after sterilization. (R&D Memorandum on PA Mesh Assessments for TVTO-PA, ETH.MESH.09922570.)

Plaintiffs' experts sometimes suggest or claim that the Prolene mesh is carcinogenic, but there is no reliable scientific evidence to support the theory or claim that polypropylene can cause cancer or sarcoma. In the more than 1,000 cases in which I have implanted one of the TVT family of products, I have not seen a single case of cancer attributable to the mesh. The literature also refutes plaintiffs' experts' suggestion or claim. (King AB, et al. Is there an association between polypropylene midurethral slings and malignancy? Urology. 2014 Oct;84(4):789–92; King AB, Goldman HB. Current controversies regarding oncologic risk associated with polypropylene midurethral slings. Curr Urol Rep. 2014 Nov;15(11):453; Linder BJ, et al. Evaluation of the local carcinogenic potential of mesh used in the treatment of female

stress urinary incontinence. Int Urogynecol J. 2016 Feb 10. doi: 10.1007/s00192-016-2961-4.) The medical literature contains no case reports of tumors caused by or associated with polypropylene implantation despite the fact that polypropylene has been implanted in millions of people. (AUGS & SUFU. Frequently Asked Questions by Providers—Mid-urethral Slings for Stress Urinary Incontinence (Mar. 12, 2014) (available at http://www.augs.org/p/bl/et/blogaid=194).)

The mesh used in the TVT, TVT-O, TVT-Abbrevo, and TVT-Exact slings is the most commonly used mesh for treatment of stress urinary incontinence and is state of the art. Many long- and intermediate-term studies consistently show that the TVT and TVT-O—and the mesh used in those devices as well as in the TVT-Abbrevo and TVT-Exact devices—are safe and effective and the standard of care for surgical treatment of SUI. (Serati M, et al. TVT for the Treatment of Urodynamic Stress Incontinence: Efficacy and Adverse Effects at 13-Year Follow-Up. Neurourol and Urodyn. 2015 Oct 19. doi: 10.1002/nau.22914; Groutz A, et al. Long-Term Outcome of Transobturator Tension-Free Vaginal Tape: Efficacy and Risk Factors for Surgical Failure. J Womens Health (Larchmt). 2011 Oct;20(10):1525–1528; Laurikainen E, et al., Five-year Results of a Randomized Trial Comparing Retropubic and Transobturator Midurethral Slings for Stress Incontinence. Eur Urol. 2014 Jun;65(6):1109–14; Athanasiou S, et al. Seven years of objective and subjective outcomes of transobturator (TVT-O) vaginal tape: Why do tapes fail? Int Urogynecol J. 2014 Feb;25(2):219–225; Serati M, et al. TVT-O for the Treatment of Pure Urodynamic Stress Incontinence: Efficacy, Adverse Effects, and Prognostic Factors at 5-Year Follow-up. Eur Urol. 2013 May;63(5):872–78; Liapis A, et al. Efficacy of inside-out transobturator vaginal tape (TVTO) at 4 years follow up. Eur J Obstet Gynecol Reprod Biol. 2010 Feb;148(2):199–201; Angioli R, et al. Tension-Free Vaginal Tape Versus Transobturator Suburethral Tape: Five-Year Follow-up Results of a Prospective, Randomised Trial. Eur Urol. 2010 Nov;58(5):671–677; Cheng D, Liu C. Tension-free vaginal tape-obturator in the treatment of stress urinary incontinence: a prospective study with five-year follow-up. Eur J Obstet Gynecol Reprod Biol. 2012 Apr;161(2):228–231; Heinonen P, et al. Tension-free vaginal tape procedure without preoperative urodynamic examination: long-term outcome. Int J Urol. 2012 Nov;19(11):1003–9; Aigmueller T, et al. Ten-year follow-up after the tension-free vaginal tape procedure. Am J Obstet Gynecol. 2011 Nov;205(5):496.e1–5; Olsson I, et al. Long-term efficacy of the tension-free vaginal tape procedure for the treatment of urinary incontinence: a retrospective follow-up 11.5 years post-operatively. Int Urogynecol J. 2010 Jun;21(6):679–683; Liapis A, et al. Long-term efficacy of tension-free vaginal tape in the management of stress urinary incontinence in women: efficacy at 5- and 7-year follow-up. Int Urogynecol J Pelvic Floor Dysfunct. 2008 Nov;19(11):1509–1512; Svenningsen R, et al. Long-term follow-up of the retropubic tension-free vaginal tape procedure. Int Urogynecol J. 2013 Aug;24(8):1271–8; Chêne G, et al. Long-term results of tension-free vaginal tape (TVT) for the treatment of female urinary stress incontinence. Eur J Obstet Gynecol Reprod Biol. 2007 Sep;134(1):87–94; Bjelic-Radisic V, et al. Patient-related Outcomes and Urinary Continence Five Years After the Tension-Free Vaginal Tape Operation. Neurourol Urodyn. 2011;30(8):1512–1517; Wu JY, et al. Surgical therapies of female stress urinary incontinence: experience in 228 cases. Int Urogynecol J. 2010 Jun;21(6):645–649; Song PH, et al. The 7-year outcome of the tension-free vaginal tape procedure for treating female stress urinary incontinence. BJU Int. 2009 Oct;104(8):1113–1117; Kuuva N, Nilsson CG. Long-term results of the tension-free vaginal tape operation in an unselected group of 129 stress incontinent women. Acta Obstet Gynecol Scand. 2006;85(4):482–

487; Celebi I, et al. Results of the tension-free vaginal tape procedure for treatment of female stress urinary incontinence: a 5 year follow-up. Arch Gynecol Obstet. 2009 Apr;279(4):463–467; Prien-Larsen JC, Hemmingsen L. Long-term outcomes of TVT and IVS operations for treatment of female stress urinary incontinence: monofilament vs. multifilament polypropylene tape. Int Urogynecol J. 2009 Jun;20(6):703–709; Jelovsek JE, et al. Randomized trial of laparoscopic Burch colposuspension versus tension-free vaginal tape: long-term follow up. BJOG. 2008 Jan;115(2):219–225; McCracken GR, et al. Five Year Follow-up Comparing Tension-Free Vaginal Tape and Colposuspension. Ulster Med J. 2007 Sep;76(3):146–149.)

The incidence of mesh exposure is low, but varies in studies between 1 and 5%. A short version Cochrane Review in 2011 observed that the monofilament synthetic midurethral slings—such as the TVT, TVT-O, TVT-Abbrevo, and TVT-Exact—were more efficacious and were associated with a lower rate of erosion than multifilament non-type-1 meshes. (Ogah J, Cody DJ, Rogerson L. Minimally invasive synthetic suburethral sling operations for stress urinary incontinence in women: a short version Cochrane review. Neurourol Urodyn. 2011 Mar;30(3):284–91.) Mesh exposure is usually asymptomatic, can cause a vaginal discharge and possibly cause coital discomfort in the male partner. Management can be topical application of vaginal estrogen or excision under local anesthetic in the office. Removal of the exposed mesh can still provide continence 80–90% of the time. (Klutke C, et al. Urinary retention after tension-free vaginal tape procedure: incidence and treatment. Urology. 2001 Nov;58(5):697–701.) While mesh-related complications can occur after placement of a polypropylene sling, the rate of such complications is acceptably low. The rate of reoperation has consistently reported to be approximately 2–5% for voiding dysfunction and exposure after a decade or more of follow-up in various studies, meta-analyses, and database reviews. (Welk B, et al. Removal or Revision of Vaginal Mesh Used for the Treatment of Stress Urinary Incontinence. JAMA Surg. 2015 Dec;150(12):1167–75; Unger CA, et al. Indications and risk factors for midurethral sling revision. Int Urogynecol J. 2016 Jan;27(1):117–22; Schimpf MO, et al. Sling surgery for stress urinary incontinence in women: a systematic review and metaanalysis. Am J Obstet Gynecol. 2014;210:1.e1–1.e27; Laurikainen E, et al. Five-year Results of a Randomized Trial Comparing Retropubic and Transobturator Midurethral Slings for Stress Incontinence. Eur Urol. 2014 Jun;65(6):1109–14; Jonsson Funk M, et al. Sling revision/removal for mesh erosion and urinary retention: long-term risk and predictors. Am J Obstet Gynecol. 2013 Jan;208(1):73.e1–7; Svenningsen R, et al. Long-term follow-up of the retropubic tension-free vaginal tape procedure. Int Urogynecol J. 2013 Aug;24(8):1271–8; Nguyen JN, et al. Perioperative complications and reoperations after incontinence and prolapse surgeries using prosthetic implants. Obstet Gynecol. 2012 Mar;119(3):539–546; Ogah, J., Cody, JD, Rogerson, L. Minimally invasive synthetic suburethral sling operations for stress urinary incontinence in women. Cochrane Database Syst Rev. 2009 Oct 7, Issue 4. Art. No.: CD006375. doi: 10.1002/14651858.CD006375.pub2; Novara G, et al. Complication Rates of Tension-Free Midurethral Slings in the Treatment of Female Stress Urinary Incontinence: A Systematic Review and Meta-Analysis of Randomized Controlled Trials Comparing Tension-Free Midurethral Tapes to Other Surgical Procedures and Different Devices. Eur Urol. 2008 Feb;53(2):288–308.)

V. The TVT, TVT-O, TVT-Abbrevo, and TVT-Exact Instructions for Use and Other Educational Materials

a. Ethicon's Instructions for Use

The instructions for use (IFU) included with the devices are specific in detail to allow the safe deployment of the devices. The procedures are adequately described such that a trained and experienced physician could implant the devices safely and effectively. The indications are adequately described in terms of patient selection and contraindications for surgery. The contraindications and warnings are adequately described based on my experience and review of the literature. The IFU is not intended to teach surgical technique, which is assumed to have been in the skill set of the surgeon. Every pelvic surgeon should be aware of the intraoperative and post-operative risks inherent. A surgeon need not be taught the entire practice of medicine in an IFU. The totality of surgical risks of pelvic floor surgeries is not included in the IFU for gynecologists or urologists and does not need to be, as the risks of anti-incontinence surgery are commonly known to surgeons. (21 C.F.R. Part 801(c); FDA Device Labeling Guidance #G91-1 (blue book memo); Ethicon Franchise Regulatory Labeling Guidance § 6.1.2 ("Labeling must convey the information that end-users need to safely use the device as intended by the manufacturer, taking into account the conditions of use and any issues that may be specific to the type of device.") Surgeons have training from numerous sources—medical school, residency, maybe fellowships, colleagues' experiences, their own experience, literature, etc.—all of which provide information regarding the risks of incontinence treatments specifically or surgery in general. (Accreditation Council for Graduate Medical Education Program Requirements for Graduate Medical Education in Female Pelvic Medicine and Reconstructive Surgery Pt. IV.A.5.b).(2).(c) (noting that fellows completing the F2 year must demonstrate competence in their knowledge of indications, contraindications, limitations, complications, techniques, and interpretation of results of screening, diagnostic, and therapeutic procedures including surgery for pelvic organ prolapse and urinary incontinence); AUGS Resident Learning Objectives (noting that residents should understand the benefits, risks, and expected outcomes of nonsurgical and surgical management of SUI); American Board of Obstetrics and Gynecology, Inc. Guide to Learning in Female Pelvic Medicine and Reconstructive Surgery 2012 (noting that fellows will perform and describe the indications, intra and postoperative complications, and success of incontinence procedures including synthetic retropubic and transobturator slings).) The IFU is used by the surgeon to become familiar with the specific device, the handling, placement and deployment in the manner that maximizes safety and efficacy. The IFU is never assumed to be a completely comprehensive list of all the possible adverse complications that are low prevalence. The IFU is intended to guide the surgeon to perform the procedure as the device was designed.

Mesh exposure and erosion are the only unique risks to mesh surgeries, and are essentially wound complications. Wound complications can also occur with other surgeries. Mesh exposure can be caused by poor quality tissue due to atrophic vaginitis, history of pelvic radiation therapy, too superficial dissection prior to sling placement, hematoma, and early sexual activity. The IFUs advise surgeons that:

- Failure to follow instructions may result in improper functioning of the device and may lead to injury.
- It's not a comprehensive reference to surgical technique for treating SUI.
- The device should only be used by physicians trained in the surgical treatment of SUI and specifically in implanting the device.
- All information should be read carefully prior to performing this procedure.

The IFU package insert is included with each device and is used as a guide for the surgeon to use the device in the manner it is intended. The IFU lists indications for use, contraindications, most prevalent risks, and the detailed description of how to deploy the device safely. IFUs in general are not intended to list every possible adverse event or post-operative complication. The IFU is generally understood to be a guide in the proper deployment of the device. Surgeons are trained in residency how to manage vaginal surgery with anatomy, handling of tissues, defining surgical planes, and perioperative care. The IFU functions to describe how this particular device is best deployed, but the patient selection, preoperative informed consent, perioperative management, and post-operative care of the patient is the surgeon's responsibility. The patient's degree of severity of vaginal prolapse and stress incontinence, with consideration of patient age, tissue integrity, previous pelvic surgery, health status, tobacco usage, and steroid or opioid dependency leads the surgeon to make a complex decision about surgical approach and the likelihood of success.

b. Ethicon's Training Programs

Ethicon began offering didactic training programs for the TVT in 1999 and later for pelvic prolapse repair when both Gynemesh and Prolift became available. The programs include didactic lectures followed by hands-on cadaver labs with experienced pelvic surgeons at each cadaver station guiding the use of the devices with step-by-step instructions about the use of the products. The didactic lectures are provided by faculty members invited from academia and private practice with extensive backgrounds in pelvic surgery and the use of Ethicon products. The programs include discussions about disease state, indications for surgery, contraindications, avoidance of complications, and the safe use of the products. Every course included a discussion of management of complications and questions from the audience. Webinars, and telesurgery programs were also offered for surgeons that previously attended cadaver labs, or were for advanced users to become familiar with the newer devices, and for dissemination of information on longer-term results when new papers were published. The preceptors are independent of Ethicon, are required to teach the courses in compliance with the slide set provided so as not to advocate or discuss any off-label uses of the products. I began as a preceptor in 2000 with the TVT and later TVT-O, TVT-Abbrevo, TVT-Secur, Prolift, and Prosima devices. I was thoroughly familiar with the products having performed the surgeries in my own practice. Contributing as a preceptor is professionally fulfilling, as it requires that I remain current in the field, and have the opportunity to collaborate with experts both nationally and internationally. There is a lack of opportunity for surgeons to learn and train on new technologies outside of residency, and Ethicon provided resources that are much appreciated by those pelvic surgeons who would like to stay current and improve their patient outcomes. Each course collected anonymous questionnaires and feedback from the attendees rating the quality of the course and proctors, including whether they felt there was commercial bias. Overwhelmingly, the response

was positive, and those proctors that were not received well were disinvited to teach future courses. The faculty has the opportunity to discuss surgical techniques and management of possible complications prior to each course.

Even after a surgeon attends a course, no certification can be provided that will ensure credentialing at their respective hospitals. Each hospital has a surgery committee that reports to the credentials committee that grants privileges for specific procedures. Surgeons must demonstrate previous training through residency, and the quality assurance department will track patient outcomes and complications. Hospitals vary in their requirements for credentialing, which includes proctoring and/or close surveillance of outcomes for new technologies or procedures. The medical device industry can provide education and training, but does not grant privileges for the use of their products. Surgeons are granted privileges based on the background training, residency director recommendations, and review of malpractice history and National Data Bank files. When credentials committees grant privileges for a specific area, they will not state specific proprietary procedures, but rather generalized areas such as cystourethropexies rather than MMK procedures or the Burch procedure.

c. Ethicon's Patient Brochures

Ethicon's Patient brochures provide information about the medical condition of incontinence, the different types, and treatment options ranging from behavior modification with pelvic exercises, electrical stimulation, medications, and bulking agents, to surgery. The information provided gives general terminology of the disease state, possible causes, and symptoms, as well as diagnosis and treatment options. The brochures are not intended to be in-depth and comprehensive, but rather to serve as a reference along with the website to pursue further information if desired. A list of contraindications for surgery is also included. The description of the procedure includes the most frequently encountered possible adverse events and repair options. The brochures are not intended and have never been used in my practice to serve as the only source of preoperative informed consent. Patients are separately informed about the indications, alternative treatments, and description of how the mesh sling will be implanted. Risks of bleeding, infection, bowel or bladder injury, persistent incontinence, retention, and pain are discussed. The possibility of mesh exposure or erosion is also discussed with re-operative repair techniques or application of vaginal cream. The information clearly states to discuss any questions with the surgeon and also provides a toll-free number to call to discuss questions with an on-call nurse.

VI. The Design of the TVT, TVT-O, TVT-Abbrevo, and TVT-Exact Devices

a. The Usefulness, Desirability, and Safety of the Devices

Prior to the availability of the TVT family of products in the U.S., surgery for stress incontinence had been more morbid and less predictable in surgical treatment outcomes. Patients who have undergone open suspensions such as a Burch procedure that have failed are reluctant to undergo reoperation due to the long and painful recovery from the open repair. Surgeries that attempt to pull up and fix the urethra and bladder neck to the pubic bone require a more extensive surgical dissection, which increases blood loss, operative time, require larger incisions,

and could cause damage to the neurovascular support of the bladder neck and urethra. Suspending procedures such as the Stamey, Peyrera, and Raz needle suspensions have been abandoned over the years due to high failure rates. The introduction of a new theory of continence by Petros and Ulmsten in the 1990s, called the integral theory, changed the approach to continence from obstructive to stabilizing the bladder neck and urethra.

The TVT, TVT-O, TVT-Abbrevo, and TVT-Exact slings are implanted via tiny incisions and the mesh slings are placed under no tension. The procedures can be performed as an outpatient under local anesthesia. The procedures do not routinely require catheterization post operatively, and can be routinely performed in under 30 minutes. Continence can be tested during the procedures. They are outpatient procedures with discharge in 3–4 hours. There is little pain, and many patients do not even need pain meds. Persistent or chronic pain occurs rarely. A recent systematic review and meta-analysis indicated that persistent or chronic pain occurs in 0.3% of retropubic midurethral sling patients, and 1.2% of trans-obturator midurethral sling patients. (Tommaselli GA, et al. Medium-term and long-term outcomes following placement of midurethral slings for stress urinary incontinence: a systematic review and metaanalysis. Int Urogynecol J. 2015 Sep;26(9):1253–68.) Most women can drive a car the next day, resume working within two days, and return to normal exercise in just one week. The large pore size allows rapid tissue incorporation and is anchorless, which decreases post-operative pain and voiding dysfunction. Because there are no anchoring sutures or fixation screws, there is no possibility of local bone pain or infection. The design of the covering sheath provides protection to the mesh during deployment and de-tensioning, reducing the risk of infection and distortion of the sling. The technique has a quarter-inch incision in the vagina requiring one suture to close and two exit puncture sites that can be sealed with a Band-Aid.

The success rates for TVT are consistently 80–95% with studies carried out up to 17 years. TVT can be performed safely in women of advanced age, and is the ideal procedure for previously failed incontinence surgeries and even the most severe Type 3 intrinsic sphincteric incontinence. The midurethral slings can be deployed either retropubic or transobturator, providing a versatility that expands the indications for use. Either approach avoids an abdominal incision and extensive surgical dissection required by fascial slings and the Burch procedure.

The mesh used in the TVT, TVT-O, TVT-Abbrevo, and TVT-Exact devices is a macroporous polypropylene monofilament knitted weave that is soft, elastic, and well-tolerated by the body, which incorporates the material and becomes a permanent support structure that allows fibroblastic and collagen deposition to provide a new neoligament supporting the mid urethra. The polypropylene monofilament has been safely used in surgery as suture throughout the body for over 40 years, and has been shown to be stable and does not degrade in the body over time. Implantation of the TVT, TVT-O, TVT-Abbrevo, and TVT-Exact is easy to teach and readily learned by both residents and experienced surgeons with reproducibility. Furthermore, the popularity of the devices has led to a greater number of Urologists and Gynecologists offering incontinence treatment to an increasing number of women.

Unlike the Burch or fascial sling, the TVT family of products come with instructions for use, a tracking lot number for safety and batch analysis, as well as MDR reporting and FDA analyses. The devices are not met with cultural or religious objections like allografts or

xenografts, and are extremely effective and durable with very low recurrence rates in patients aged 30–80 years. There is a positive net effect on overactive bladder symptoms with improvement in one-third to one-half of patients after TVT. Additionally, there is a net positive effect on sexual function—no more urinating during intercourse and consistent improvement in validated quality-of-life questionnaires. A 2012 study with 2-year follow-up that looked at sexual function and activity following midurethral sling placement reported significant improvements in sexual function after both retropubic and transobturator sling procedures. Dyspareunia, incontinence during sex, and fear of incontinence during sex all improved significantly after surgery. (Zyczynski HM, et al. Sexual activity and function in women more than 2 years after midurethral sling placement. Am J Obstet Gynecol. 2012 Nov;207(5):421.e1–6.) In fact, one recent systematic review and meta-analysis found that dyspareunia following implantation of retropubic and transobturator midurethral slings was rare. (Schimpf MO, et al. Sling surgery for stress urinary incontinence in women: a systematic review and metaanalysis. Am J Obstet Gynecol. 2014;210:1.e1–1.e27.)

TVT has more RCTs and long-term data than any other incontinence treatment. The TVT, TVT-O, TVT-Abbrevo, and TVT-Exact are easily studied, patients can be counseled on the vast data, and the study data can be compared to other products and surgical approaches. It is comforting as a surgeon to be using a product that is known to have the largest amount of peer-reviewed data from multiple institutions substantiating a safe, reliable, reproducible technique and material. Prolene has been around for 50 years, been safely used in various applications, and the body's reaction to the material is known. Moreover, surgeons desire polypropylene slings, as over 90% of meshes for SUI are polypropylene. The favored approach is transvaginal, midurethral, and supported by all the specialty societies.

The design optimizes safety by avoiding the large abdominal incision needed for a Burch and fascial sling: a 1.5-cm vaginal incision compared to a 6- to 8-inch abdominal incision for a Burch, or multiple incisions for a fascial sling. The trocars used to pass the sling are tapered with a blunt tip so as to pass through the tissues atraumatically as compared to Stamey needles, which are sharper. Passage of the trocars through the retropubic space has been performed for 50 years, and surgeons are familiar with the anatomy. Complications are usually surgery-related and not mesh-specific. Bladder injury occurs in less than 5% of patients, and occurs as a result of trocar passage, which is managed by re-passage of the trocar and placement of a catheter for 24 hrs. The bladder puncture heals rapidly and completely. Plaintiffs' experts may contend that the trocars are passed "blindly" and that that is unsafe. But the use of cystoscopy insures that the trocar passages have not perforated the bladder. Multiple cadaver studies show that with proper technique, trocars are passed within an anatomic margin of safety. The design of the helical passers used with the TVT-O and TVT-Abbrevo is such that it avoids neurovascular structures. Furthermore, bladder and bowel perforation can occur with the Burch procedure or fascial sling procedures as well. I have directly observed post-Burch bladder perforations of the sutures causing infection, bleeding, and stone formation.

Exposures are uncommon and manageable, occurring in about 1–3% of cases. The cause can be poor tissue integrity caused by estrogen deficiency, delayed wound healing due to diabetes, steroid usage, hematoma formation, or placing the sling too superficially. Treatment includes application of topical estrogen cream, re-closure of the mucosal edges, and limited mesh

excision if necessary. The excision can be performed in an office setting under local anesthesia or under light sedation in an OR. Dyspareunia is rare because the slings' design positions the mesh placement under the midurethra, via the distal anterior wall incision, at a part of the vaginal wall where the forces and stress from penile contact are minimal. And the design of the TVT and TVT-Exact provides for the mesh sling to traverse up (vertically) away from the vagina, while the design of the TVT-O and TVT-Abbrevo provides for the mesh sling to traverse laterally away from the vagina.

Obstructive voiding dysfunction occurs in less than 10% of cases and can be readily managed by either opening the incision in the first few days and loosening the sling or waiting 3–4 weeks to incise the sling under local anesthetic. Continence is preserved 90% of the time. Contrarily, an obstructive Burch procedure will require opening the abdominal incision and taking down the previous repair which entails a more morbid and protracted recovery with probable recurrent incontinence.

Infection is extremely rare due to the macroporous mesh allowing the immune cells—macrophages—to remove possible bacteria. (Ford AA, Rogerson L, Cody JD, Ogah J. Mid-urethral sling operations for stress urinary incontinence in women. Cochrane Database Syst Rev. 2015, Issue 7. Art. No.: CD006375. doi: 10.1002/14651858.CD006375.pub3.) Fibroblasts and blood vessel incorporation allow for tissue regeneration and incorporation of the mesh into the body. Due to the permanence of the sling, recurrent incontinence is uncommon. The inert nature of polypropylene avoids the risk of rejection and infection, which can occur with allografts and xenografts. Since the material is not biologic, there is no risk of virus or prion transmission.

Single-incision and mini slings—while appropriate, safe, and effective devices under certain circumstances—have less efficacy and far less data to support their use over full-length slings. Multifilament mesh has been previously established to be poorly tolerated by the tissues with an unacceptable infection and encapsulation rate. Larger pore mesh does not have the same support characteristics, and does not have supporting data to prove equivalence with the established Ethicon mesh that has 17-year published follow-up.

As discussed above, laser-cut mesh has no clinical difference when compared to mechanical-cut mesh in the physiologic range of stress when implanted in the female pelvis. (ETH.MESH.01784823–28 (CER Laser Cut Mesh); ETH.MESH.01222075–79 (Elongation Characteristics of Laser Cut Prolene Mesh for TVT); ETH.MESH.06696367–79 (Performance Evaluation of TVT U Prolene Mesh); Lin AT, et al. In Vivo tension Sustained by Fascial Sling in Pubovaginal Sling Surgery for Female Stress Urinary Incontinence, J Urol. 2005 Mar;173(3):894–897.) The only difference is aesthetic, and any particles lost on mechanical-cut mesh cause no harm, as it is the same Prolene used in suspension procedures, Burch or fascial sling fixations.

All surgical procedures have inherent risks. All pelvic surgeries have similar risks, and the introduction of the TVT family of products served to decrease complications when compared to previous techniques. Because native repairs and cystourethropexies do not involve a kit product, complications are not reportable to the MAUDE database. Scientific research has

provided improved materials and applications to both improve efficacy and decrease complications. Synthetic mesh that is microporous or too macroporous has proven to be either less safe or less efficacious. If the mesh is too lightweight or too large pore, there is inadequate support.

Ethicon has taken extensive steps to ensure the proper use of its products. The IFU, Surgeon's Monograph, Professional Education training, including didactic lectures and cadaver labs, proctorships, and webinars were designed to offer an extensive resource for the pelvic surgeon to learn the indications for use, surgical technique, and avoidance and management of potential complications. The combination of residency training, previous surgical and clinical experience, and the training resources provided by Ethicon led to many pelvic surgeons gaining expertise in the use of its products, which continues to this day.

All pelvic surgery has similar and inherent risks. Pelvic floor surgeons should be and are aware of the potential complications involved with any surgical treatment of SUI based on a combination of their medical school education, their residencies, fellowships, their experience, their continuing education, and their review of the device's IFU if a device is used. Risks such as infection, scarring, inflammation, bladder damage, bowel damage, ureter damage, nerve damage, injury to vessels, wound complications (such as wound dehiscence, herniation, hematoma, seroma, pelvic abscess, exposure, and erosion), pain, pelvic pain, groin pain, dyspareunia, fistula, anesthetic risks, bowel or bladder dysfunction, failure of the operation, bleeding, death, pulmonary embolism, myocardial infarction, pneumonia, deep vein thrombosis, and need for reoperation are basic elemental surgical risks of any pelvic floor surgery involving mesh. Surgeons understand that these complications can happen, and they also understand that the symptoms can range in terms of severity and duration.

Surgeons are expected to understand the anatomy in which they are operating, and should identify and dissect in safe planes, avoiding inadvertent damage to the organs and vessels contained within the pelvis. The education and training of the pelvic surgeon should be adequate to know the possibility of complications and their avoidance, risks of recurrence and reoperation. Indeed, the development of biologic and synthetic materials was motivated by the high failure rate of pelvic reconstruction due to the weakness of the patients' connective tissue leading to the condition requiring repair. There is an extensive body of medical knowledge in the medical literature discussing the possibility of complications with the use of meshes. Surgeons' prior experience with mesh informs their understanding of potential complications with pelvic floor surgeries, including those involved with mesh devices. While mesh exposure is unique to mesh devices, it is obvious, and it is general knowledge within female urology and urogynecology. The potential injury to vessels and organs caused by trocars is well-known to surgeons, and potential mesh exposure and foreign body reactions are common knowledge.

Furthermore, the FDA issued a Public Health Notification in 2008 regarding the use of synthetic mesh for treatment of prolapse and incontinence. It alerted healthcare practitioners to "complications associated with transvaginal placement of surgical mesh to treat Pelvic Organ Prolapse (POP) and Stress Urinary Incontinence (SUI)." It noted that the complications were rare, but could have serious consequences, and that the "most frequent complications included erosion through the vaginal epithelium, infection, pain, urinary problems, and recurrence of

prolapse and/or incontinence." It also noted that there were "reports of bowel, bladder, and blood vessel perforation during insertion," and that "[i]n some cases, vaginal scarring and mesh erosion led to a significant decrease in patient quality of life due to discomfort and pain, including dyspareunia." This Public Health Notification was yet another source of knowledge for surgeons regarding potential complications associated with synthetic mesh midurethral slings, complementing the TVT, TVT-O, TVT-Abbrevo, and TVT-Exact's IFUs, Ethicon's professional education seminars, and the surgeons' training, education, and experience.

Based upon the analysis above, and on my education, my training, my experience using these products and alternative incontinence treatments, and my reading of the literature referenced above, I believe the TVT, TVT-O, TVT-Abbrevo, and TVT-Exact slings are not defective, but are reasonably safe for their intended use and have a positive benefit-to-risk profile; better than the Burch and native tissue slings. In my opinion, the benefits of the TVT, TVT-O, TVT-Abbrevo, and TVT-Exact slings far outweigh the risks of using the devices. The devices are the gold standard and standard of care for treating stress urinary incontinence. At the time the products were launched, I do not believe they could have been made safer for their intended use. The products were state of the art at the time they were launched, and remain so today.

Date: 1/4/17

Douglas H. Grier, M.D.

UNITED STATES DISTRICT COURT
SOUTHERN DISTRICT OF WEST VIRGINIA
CHARLESTON DIVISION

IN RE: ETHICON, INC., PELVIC REPAIR SYSTEM PRODUCTS LIABILITY LITIGATION	**Master File No. 2:12-MD-02327** **MDL 2327** **JOSEPH R. GOODWIN** **U.S. DISTRICT JUDGE**
THIS DOCUMENT RELATES TO: *Wave 11 Cases*	

GENERAL EXPERT REPORT OF DOUGLAS H. GRIER, M.D.

UNITED STATES DISTRICT COURT
SOUTHERN DISTRICT OF WEST VIRGINIA
CHARLESTON DIVISION

IN RE: ETHICON, INC., PELVIC REPAIR SYSTEM PRODUCTS LIABILITY LITIGATION	**Master File No. 2:12-MD-02327** **MDL 2327** **JOSEPH R. GOODWIN** **U.S. DISTRICT JUDGE**
THIS DOCUMENT RELATES TO: *Wave 6 Cases*	

EXPERT REPORT OF DOUGLAS H. GRIER, M.D.

Report re TVT, TVT-O, TVT-Exact, and TVT-Abbrevo Midurethral Slings

Douglas H. Grier, M.D.
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This report contains a summary of my qualifications, education, training and experience, a statement of my opinions that I have formed to date, the bases for those opinions, and the information I considered in forming my opinions. All of my opinions are based on my education, training, clinical experience, the pertinent medical literature, discussions with colleagues, and other materials I have reviewed. Materials that support my findings and opinions, including documents that I have reviewed, are identified either in this report or are listed in the attached reliance materials list.

All of the opinions I express in this report are held to a reasonable degree of medical and scientific certainty. If I receive additional information after signing this report but before trial, I may form additional or different opinions.

I. Background

a. Education, Training, and Experience

I attended the University of Florida in Gainesville, Florida, graduating with a Bachelor of Science degree in Chemistry with High Honors in 1976. I attended medical school at George Washington University, graduating in 1982. I then did a surgical internship in 1982–1983 at the Portsmouth Naval Hospital in Portsmouth, Virginia. Following my internship, I did a urological residency at the Portsmouth Naval Hospital from 1984–1988. I served as Chief of Urology at Jacksonville Naval Hospital in 1990–1991.

Prior to my residency, I served in Operation Urgent Fury in Grenada in October 1983 and as part of the Multinational Peacekeeping Force in Beirut, Lebanon in 1983–1984. After my residency, I served in Operation Desert Shield and Operation Desert Storm with the 1st Marine Division, stationed in Saudi Arabia and Kuwait in 1990–1991.

I am the President of the Medical Staff at Swedish/Edmonds Hospital in Edmonds, Washington. I also serve as the Chair of Swedish Hospital's Medical Quality Oversight Committee, Chair of the Credentials Committee, Treasurer of the Medical Staff for the Swedish Hospital System, and as a member of the Executive Committee at Swedish Hospital.

I became a Diplomate of the American Board of Urology in 1990 and was recertified in 2010. I am an active member of the American Urological Association, the Washington State Medical Association, the Northwest Urological Society, the Washington State Urology Society, the King County Medical Society, the American Association of Clinical Urologists, the Society of Urodynamics Female Pelvic Medicine & Urogenital Reconstruction, and the International Continence Society.

My curriculum vitae is attached to this report.

b. Clinical Experience & Personal Experience with Stress Urinary Incontinence Treatments

I have a special focus in female pelvic medicine and surgery. Over the course of my career, I have performed various types of native tissue surgery and surgery utilizing mesh, including Ethicon's TVT and TVT-O, TVT-Abbrevo, TVT-Exact and TVT-Secur midurethral slings, AMS Monarch, Uretex by Bard, Vesica In Situ sling, Stamey cystourethropexy, MMK, and Burch procedures. I have also performed robotic sacrocolpopexies, as well as open abdominal sacrocolpopexies. I have also performed various types of native tissue surgeries and surgeries utilizing mesh to treat pelvic organ prolapse and hernias.

c. Teaching & Training Experience Related to Stress Urinary Incontinence

I served as a faculty member at the Ethicon Endosurgical Institute, and as a National Preceptor for Gynecare products, conducting over 300 courses for advanced surgical training of physicians for conditions such as stress urinary incontinence and pelvic organ prolapse. I have lectured to pelvic floor surgeons throughout the United States, Canada, Europe, and China. I have performed research in the field of incontinence and bladder disorders, contributing to studies on the use of TVT abdominal guides, and the TVT world registry published in the Journal of Urology in 2011. I was also an investigator in an FDA trial of a pelvic nerve stimulator for the treatment of urge incontinence.

d. Litigation Consulting Work

During the previous four years, I have testified as an expert witness at trial or by deposition in the following cases:

- Perry v. Ethicon, Inc., et al.—Bakersfield, CA
  - Deposition Testimony on 12/30/14
  - Trial Testimony on 02/17/15, 02/18/15, and 02/19/15
- Daino v. Ethicon and Hill v. Ethicon—
  - Deposition Testimony on 3/29/16
- Freitas v. Ethicon; Ruiz v. Ethicon; Bartlett (Pratt) v. Ethicon; Hankins v. Ethicon; Gray-Wheeler v. Ethicon, Barbara A. Hill v. Ethicon, Daino v. Ethicon,—
  - Deposition Testimony on 3/22/16
- Lambert v. Ethicon; Lenz v. Ethicon; Lewis-McCann v. Ethicon; Majors v. Ethicon—
  - Deposition Testimony on 7/13/16
- In re: Ethicon, Inc. Pelvic Repair System Products Liability Litigation
  - Deposition Testimony on 8/23/16 (Prosima general report)
  - Deposition Testimony on 8/23/16 (TVT Exact general report)
- Conley v. Ethicon; Currie v. Ethicon
  - Deposition Testimony on 8/23/16

I am being compensated $500 per hour for my study and testimony in this case.

II. Stress Urinary Incontinence

a. Definition, Mechanism of Action, and Prevalence

Urinary incontinence is the involuntary leakage of urine, and can take different forms such as urge incontinence, stress incontinence, or mixed incontinence. Urinary incontinence affects up to 50% of women at some point in their lives. (Ford AA, Rogerson L, Cody JD, Ogah J. Mid-urethral sling operations for stress urinary incontinence in women. Cochrane Database Syst Rev. 2015, Issue 7. Art. No.: CD006375. doi: 10.1002/14651858.CD006375.pub3.) Stress Urinary Incontinence ("SUI") is the involuntary leakage of urine during activities such as coughing, sneezing, lifting, laughing, or exercising. (IUGA. Stress Urinary Incontinence – A Guide for Women.) The proposed mechanism of action for the development of stress urinary incontinence is weakening of the pubourethral ligaments and loss of intrinsic sphincter tone.

SUI is diagnosed by bladder questionnaire, examination, cough test, bladder diary, urodynamic studies, and cystoscopy. Pelvic organ prolapse, overactive bladder, and urinary incontinence affect more women than diabetes, heart disease, or arthritis. SUI is a very common condition, and affects at least 10–35% of women. (IUGA. Stress Urinary Incontinence – A Guide for Women; Dooley Y, et al. Urinary incontinence prevalence: results from the National Health and Nutrition Examination Survey. J Urol. 2008 Feb;179(2):665–661.) A recent Cochrane review notes that, of the 50% of women who will experience urinary incontinence at some point in their lives, 30–80% experience SUI. (Ford AA, Rogerson L, Cody JD, Ogah J. Mid-urethral sling operations for stress urinary incontinence in women. Cochrane Database Syst Rev. 2015, Issue 7. Art. No.: CD006375. doi: 10.1002/14651858.CD006375.pub3.) Moderate-to-severe SUI affects women at an increasing rate as they age, and has been reported to affect 6.9% of women 20–39 years old, 17.2% of women 40–59 years old, 23.3% of women aged 60–79 years, and 31.7% of women 80 years or older. (Nygaard I, et al. Prevalence of symptomatic pelvic floor disorders in US women. JAMA. 2008 Sep 17;300(11):1311–1316.) One study estimated that approximately 11% of women will have surgery to treat either SUI or pelvic organ prolapse in their lifetime. (Olsen AL, et al. Epidemiology of surgically managed pelvic organ prolapse and urinary incontinence. Obstet Gynecol. 1997;89:501–506.) Over 200,000 surgeries are performed in the U.S. for the treatment of SUI and pelvic organ prolapse each year. (Gerten KA, et al. Prolapse and incontinence surgery in older women. J Urol. 2008 Jun;179(6):2111–2118.)

b. Risk Factors for Stress Urinary Incontinence

Smoking: Women who smoke are 1.8–2.9 times more likely to develop SUI. (Bump RC, McClish DK. Cigarette smoking and urinary incontinence in women. Am J Obstet Gynecol. 1992 Nov;167(5):1213–1218.) Smoking can lead to COPD, which increases abdominal pressures through chronic coughing.

Obesity: Increasing body mass index correlates to an increase in the symptoms of urinary incontinence and pelvic organ prolapse through the mechanism of increased intravesical pressure and bladder receptor changes. (Hannestad YS, et al. Are smoking and other lifestyle factors associated with female urinary incontinence? The Norwegian EPINCONT Study. Br J Obstet Gynaecol. 2003 Mar;110(3):247–254.) Obese women have a 4.2-fold greater risk of developing SUI compared to women with an average BMI. (ACOG / AUGS Practice Bulletin No. 155; Nov. 2015.)

Menopause: Decreasing serum levels of estrogen are known to increase the incidence of both stress incontinence and integrity of the pubocervical fascia of the vagina by decreasing vascularity and thickness of the tissues. Postmenopausal decreased estrogen levels lead to urogenital atrophy with the increased risk of infections of the urinary tract and changing of the vaginal pH. (Siddighi S, Hardesty JS. Urogynecology & Female Pelvic Reconstructive Surgery. ISBN 0-07-144799-7.)

Pregnancy and Childbirth: Damage sustained to the muscles and nerves of the pelvic floor significantly increases the risk of both stress and urge incontinence and pelvic organ prolapse. A woman with three or more vaginal deliveries has an 11-fold increased risk of pelvic organ prolapse compared to a nulliparous woman. The weight of the infant contributes to prolapse with an increase of 10% per pound weight of the infant. (Siddighi S, Hardesty JS. Urogynecology & Female Pelvic Reconstructive Surgery. ISBN 0-07-144799-7.)

Chronic Constipation and Heavy Lifting: Chronic constipation and heavy lifting cause increased pelvic pressures which lead to increased fascial stress over time.

Race: Increasing incidence of SUI occurs from Asian women < African-American women < Caucasian Women. Caucasian women have the highest risk of pelvic organ prolapse. (Siddighi S, Hardesty JS. Urogynecology & Female Pelvic Reconstructive Surgery. ISBN 0-07-144799-7.)

Age: The mean age for SUI in women is 48 years, for mixed incontinence in women 55 years, and urge incontinence in women is 61 years. The prevalence of incontinence is 39.6 million women as of 2001. (Siddighi S, Hardesty JS. Urogynecology & Female Pelvic Reconstructive Surgery. ISBN 0-07-144799-7.)

Congenital Factors: Women with prolapse tend to have an abundance of the weaker type III collagen in the pubocervical fascia with a higher degree of joint hypermobility with associated collagen vascular disorders. These factors also increase the incidence and severity of prolapse. Collagen vascular diseases have been implicated in the development of SUI and pelvic organ prolapse. (Siddighi S, Hardesty JS. Urogynecology & Female Pelvic Reconstructive Surgery. ISBN 0-07-144799-7.)

Pelvic Organ Prolapse: 62% of women with prolapse also report SUI and 63% of women with stress incontinence have associated prolapse. (Siddighi S, Hardesty JS. Urogynecology & Female Pelvic Reconstructive Surgery. ISBN 0-07-144799-7.)

c. Economic Impact and Impact on Quality of Life

Women who develop urinary incontinence adapt by minimizing activities, wearing incontinence diapers, and by avoiding social interactions and sexual relationships due to fear of embarrassment. (Fultz NH, et al. Burden of stress urinary incontinence for community-dwelling women. Am J Obstet Gynecol. 2003 Nov;189(5):1275–1282.) It has been reported that less than half of women who experience incontinence tell their healthcare providers about their symptoms. (Wu JM, et al. Prevalence and incidence of urinary incontinence in a diverse population of women with noncancerous gynecologic conditions. Female Pelvic Med Reconstr Surg. 2010;16(5):284–289; ACOG / AUGS Practice Bulletin No. 155; Nov. 2015.) The impact of decreased physical activities for fear of incontinence leads to cardiovascular deconditioning, further obesity, and social isolation. The incontinence also increases the incidence of urinary tract infections, which can lead to kidney infections and hospitalizations. The symptoms of SUI can also increase the incidence and severity of depression.

Economic costs of urinary incontinence were estimated to be $32 billion as of 2000, with the cost derived from providing laundry, pads, and absorbent products. The majority of those costs do not come from providing treatment. The November 2015 ACOG/AUGS Practice Bulletin on Urinary Incontinence in Women notes that the "estimated direct cost of urinary incontinence care in the United States is $19.5 billion." (ACOG / AUGS Practice Bulletin No. 155; Nov. 2015.) 62% of women with prolapse also report SUI and 63% of women with stress incontinence have associated prolapse. (Siddighi S, Hardesty JS. Urogynecology & Female Pelvic Reconstructive Surgery. ISBN 0-07-144799-7; Wagner. Economic Costs of Urinary Incontinence. Urology. 1998;51:355–361.) 30% of women will undergo repeat surgery for recurrent prolapse over their lifetime.

III. Treatment Options for SUI

a. Nonsurgical Options for Treatment of Stress Urinary Incontinence

Nonsurgical treatment options for SUI are behavior modifications, including more frequent voiding, incontinence pads or briefs, biofeedback, pelvic-floor muscle exercises, weight reduction, management of fluid intake, smoking cessation, reduced intake of coffee, tea, and carbonated beverages, reduced occupational or recreational activities that require repetitive or chronic straining, and constipation management. Other nonsurgical treatment options include functional electrical stimulation (PTNS) and mechanical devices. (Siddighi S, Hardesty JS. Urogynecology & Female Pelvic Reconstructive Surgery. ISBN 0-07-144799-7; ACOG / AUGS Practice Bulletin No. 155; Nov. 2015.) Only 15–28% of women have their incontinence 100% cured by pelvic-floor muscle training (PFMT), and after a 3–15-year follow-up, 25–50% of women primarily treated with PFMT to try to improve or cure their incontinence will undergo surgery. (Labrie J, et al. Protocol for Physiotherapy OR Tvt Randomised Efficacy Trial (PORTRET): a multicenter randomised controlled trial to assess the cost-effectiveness of the tension free vaginal tape versus pelvic floor muscle training in women with symptomatic moderate to severe stress urinary incontinence. BMC Women's Health. 2009;9:24.)

Pessaries are believed to control SUI symptoms by increasing urethral resistance and supporting the urethra. They "may improve the symptoms of stress and mixed urinary incontinence, but objective evidence regarding their effectiveness has not been reported." (ACOG / AUGS Practice Bulletin No. 155; Nov. 2015.)

The limitations of nonsurgical management options are that they rarely fully restore continence, but rather help cope with the condition. There is no FDA-approved medication for the treatment of SUI. (ICS Fact Sheets: A Background to Urinary and Faecal Incontinence (July 2013); 2013 AUA SUI Patient Guide.)

b. Surgical Options for Treatment of Stress Urinary Incontinence

Because of the limitations of nonsurgical treatment options, surgery is the definitive and long-term treatment for symptomatic SUI. There are over 150 described surgical treatments for SUI. All of these surgeries have shared risks such as hematoma, bladder or bowel injury, lower urinary tract injury, vascular injury, infection, urinary retention, persistent SUI, bleeding, pain, dyspareunia, fistula, and de novo or worsening urge incontinence. (ACOG / AUGS Practice Bulletin No. 155; Nov. 2015.)

i. Native Tissue and Tension Repairs

The primary surgical native tissue and tension repairs include the Kelly plication (introduced in 1912), Pereyra needle urethropexy (introduced in 1959), and abdominal operations for SUI such as the Burch colposuspension (introduced in 1961) and Marshall Marchetti Krantz (MMK) cystourethropexy (introduced in 1949). (Siddighi S, Hardesty JS. Urogynecology & Female Pelvic Reconstructive Surgery. ISBN 0-07-144799-7.)

Retropubic trans-abdominal surgeries (Burch and MMK) when compared to TVT, are less cost-effective, more morbid, have greater operative time, and longer recovery with equal efficacy. (Ward K, et al. Prospective multi-center randomized trial of tension-free vaginal tape and colposuspension as primary treatment for stress incontinence. BMJ. 2002 Jul;325:1–7.) In a randomized controlled trial of TVT versus Burch with five-year follow-up, the procedures had similar patient satisfaction and efficacy, but the TVT group had less voiding dysfunction. (Ward K, Hilton P, on behalf of the UK and Ireland TVT Trial Group. Tension-free vaginal tape versus colposuspension for primary urodynamic stress incontinence: 5-year follow up. BJOG. 2008;115:226–233.) A 2009 Cochrane review of TVT versus Burch reported that TVT appeared to be as effective as the open Burch procedure, but associated with fewer complications, less voiding dysfunction, shorter operative times, and increased safety. (Ogah, J, Cody, JD, Rogerson, L. Minimally invasive synthetic suburethral sling operations for stress urinary incontinence in women. Cochrane Database Syst Rev. 2009, Issue 4. Art. No.: CD006375. doi: 10.1002/14651858.CD006375.pub2.) A meta-analysis of 39 RCTs published in 2010 by Novara, et al. indicated that patients receiving midurethral slings, especially TVT, while having an increased risk of bladder perforation, had significantly higher overall and objective cure rates than did the patients who had a Burch procedure. (Novara G, et al. Updated systematic review and meta-analysis of the comparative data on colposuspensions, pubovaginal slings, and

midurethral tapes in the surgical treatment of female stress urinary incontinence. Eur Urol. 2010 Aug;58(2):218–38.)

Retropubic trans-abdominal surgeries such as the Burch and MMK involve larger incisions, more dissection, are performed as inpatient rather than ambulatory procedures, and have a greater average blood loss than the midurethral sling procedures discussed below. (Chaliha C, Stanton SL. Complications of surgery for genuine stress incontinence. Br J Obstet Gynaecol. 1999 Dec;106(12):1238–45.) Data shows that long-term efficacy following Burch declines with time and plateaus at ten years with 70% cure. One in ten patients needs at least one additional surgery for correction of SUI ten years after undergoing a Burch procedure. (Alcalay. Burch colposuspension: a 10–20 year follow up. Br J Obstet Gynaecol. 1995;102:740–745.) In another long-term study of the Burch procedure, 56% of the patients studied experienced subjectively significant urinary incontinence. (Kjolhede P. Long-term efficacy of Burch colposuspension: a 14–year follow-up study. Acta Obstet Gynecol Scand. 2005, 84:767–772.) In the SISTEr study, 70% of patients undergoing the Burch procedure had treatment failure at two years' follow-up when all criteria were considered. (Albo, ME, et al. Burch Colposuspension versus Fascial Sling to Reduce Urinary Stress Incontinence. N Engl J Med. 2007;356:2143–2155.) In the extended SISTEr trial, between 2–7 years post-op, continence rates dropped from 42% to 13% in patients who had the Burch procedure. (Richter HE, et al. Patient Related Factors Associated with Long-Term Urinary Continence After Burch Colposuspension and Pubovaginal Fascial Sling Surgeries. J Urol. 2012 Aug;188(2):485–489.) A study by Demirci showed comparable trends in decreasing efficacy and late complications. Demirci reported late complications in 220 women, including enterocele (35), rectocele (32), cystocele (18), suprapubic or groin pain (15), and dyspareunia (6). (Demirci F, et al. Long-term results of Burch colposuspension. Gynecol Obstet Invest. 2001;51(4):243–7.)

Laparoscopic Burch procedures have a lower cure rate, higher complication rate, and higher operative cost than open Burch procedures. (Siddighi S, Hardesty JS. Urogynecology & Female Pelvic Reconstructive Surgery. ISBN 0-07-144799-7; Walters, Surgical management of stress incontinence, Clinical Obstetrics & Gynecology-Incontinence. Lipincott William & Wilkins 2004:93–103.) A 2012 Cochrane Review reported that there was insufficient evidence to determine whether the laparoscopic Burch procedure has an advantage over the open Burch procedure in terms of cost-effectiveness, longer-term complications, safety, quality of life, and subjective and objective cure rates. (Lapitan MC, Cody JD. Open retropubic colposuspension for urinary incontinence in women. Cochrane Database Syst Rev. 2012 Jun 13.)

In the SISTEr trial, 47% of the patients undergoing the Burch procedure experienced adverse events. (Albo, ME, et al. Burch Colposuspension versus Fascial Sling to Reduce Urinary Stress Incontinence. N Engl J Med. 2007;356:2143–2155.) Urinary retention rate after Burch is 12%. De novo detrusor overactivity is 16% post-operatively. 25–45% patients with mixed incontinence pre-op will have worse detrusor overactivity post-op. There is a 7–14% risk of enterocele (prolapsed small intestine) formation. 12% have post-colposuspension syndrome, which is chronic pain in the low- to mid-pelvis due to the Burch suture tension. (Siddighi S, Hardesty JS. Urogynecology & Female Pelvic Reconstructive Surgery. ISBN 0-07-144799-7.) Osteitis pubis—which is inflammation of the periosteum from the sutures—occurs at a rate of 2–3%. Dyspareunia increases when combined with vaginal prolapse surgery. Urinary tract

infections and wound complications also occur. (Siddighi S, Hardesty JS. Urogynecology & Female Pelvic Reconstructive Surgery. ISBN 0-07-144799-7.) The Alcalay study reported that 14.7% of the patients had detrusor instability, 22% had long-term voiding difficulty, and 4.6% had recurrent urinary tract infections. The AUA 2012 Update to the SUI Guidelines reported higher rates of pain and sexual dysfunction with the Burch procedure than with midurethral slings. (Guideline for the Surgical Management of Female Stress Urinary Incontinence: 2009 Update Appendices A11 and A16.) The significant post-operative morbidity and complications associated with the Burch procedure has caused surgeons to turn to other procedures to treat SUI. (Wu CJ, et al. The surgical trends and time-frame comparison of primary surgery for stress urinary incontinence, 2006–2010 vs 1997–2005: a population-based nation-wide follow-up descriptive study. Int Urogynecol J. 2014 Dec;25(12):1683–91; Chughtai BI, et al. Midurethral Sling Is the Dominant Procedure For Female Stress Urinary Incontinence: Analysis of Case Logs From Certifying American Urologists. Urology. 2013 Dec;82(6):1267–71; Suskind AM, et al. Effectiveness of Mesh Compared with Nonmesh Sling Surgery in Medicare Beneficiaries. Obstet Gynecol. 2013 Sep;122(3):546–52; Rogo-Gupta L, et al. Trends in the Surgical Management of Stress Urinary Incontinence Among Female Medicare Beneficiaries, 2002–2007. Urology. 2013 Jul;82(1):38–41; Nager CW, et al. A Randomized Trial of Urodynamic Testing before Stress-Incontinence Surgery. N Engl J Med. 2012 May;366(21):1987–97; Wu JM, et al. Trends in inpatient urinary incontinence surgery in the USA, 1998–2007. Int Urogynecol J. 2011 Nov;22(11):1437–43.)

Retropubic needle suspensions have been essentially abandoned due to high failure rates, and they share all of the risks discussed above with respect to retropubic trans-abdominal surgeries.

ii. Bulking Agents

Bulking agents are another option for treatment of SUI. They can be made of bovine collagen or polytetrafluoroethylene (PTFE), and are needle-injected into the urethral submucosa to coapt the urethra. Advantages of these procedures include the fact that they can be office-based, they do not require general anesthesia, they can be performed in patients who are not surgical candidates, and they can be used after failed previous surgeries. While bulking agents are invasive, they are less invasive than other surgical options. Drawbacks of bulking agents include high cost and lower cure rates—25% dry, 50% improved, and 25% requiring repeat injections. Complications include urinary retention (15–25%), urinary tract infection (5–30%), irritative voiding symptoms (less than 20%), allergic reactions (4%), and product migration. (Gross M, et al. Periurethral injections. In: Bent AE, et al., eds. Ostergard's Urogynecology and Pelvic Floor Dysfunction. 5th ed. Lippincott William & Wilkins; 2003:495–502.) "[U]rethral bulking agents are less effective than surgical procedures such as sling placement and are rarely used as primary treatment for stress urinary incontinence." (ACOG / AUGS Practice Bulletin No. 155; Nov. 2015.)

iii. Artificial Urinary Sphincters

Artificial urinary sphincters are inflatable cuffs that surround the proximal urethra and bladder neck. They provide mechanical obstruction of the urethra when inflated and allow

opening with activation of a control pump. Due to the extensive surgery required and long-term complications of device failure (e.g., pump failure, urethral erosion, infection), artificial sphincters are used for severe incontinence when other procedures have failed. (Appell. Techniques and results in the implantation of the artificial urinary sphincter in women with type 3 SUI with vaginal approach. Neurourol Urodyn. 1988;7:613–619.)

iv. Proximal Suburethral Slings

Another surgical treatment option for SUI is the proximal suburethral sling. Originally used only for intrinsic sphincter deficiency ("ISD") and recurrent stress incontinence because of the higher post-operative complications, proximal suburethral slings create a hammock underneath the urethra and bladder neck to prevent descent and provide a backboard for compression of the urethra during increased intra-abdominal pressure. First described in 1907, several biologic and synthetic materials have been used, and bone-anchored slings have also been developed. The biologic materials used include autografts (fascial tissue removed from the patient's abdomen (rectus fascia) or outer thigh (fascia lata)), allografts (sterilized fascia from a cadaver), or xenografts (sterilized fascia from an animal). Modification of the suburethral slings by anchoring to the pubic bone does not increase effectiveness, and carries an increased risk of osteomyelitis. Overall success is between 82–90% at 5 years. Cure rates for SUI with ISD at 5 years is 80–90%, which is higher than Burch. However, in the SISTEr study, 57% of patients receiving a fascial sling had treatment failure at two years' follow-up when all criteria were considered. (Albo, ME, et al. Burch Colposuspension versus Fascial Sling to Reduce Urinary Stress Incontinence. N Engl J Med. 2007;356:2143–2155.) In the extended SISTEr trial, between 2–7 years post-op, continence rates dropped from 52% to 27% in patients who had pubovaginal slings. (Richter HE, et al. Patient Related Factors Associated with Long-Term Urinary Continence After Burch Colposuspension and Pubovaginal Fascial Sling Surgeries. J Urol. 2012 Aug;188(2):485–489.) The 2014 SGS systematic review and meta-analysis by Schimpf, et al. observed that, when comparing pubovaginal slings versus midurethral slings, subjective cure was higher with midurethral slings. Therefore, the authors recommended midurethral slings over pubovaginal slings. (Schimpf MO, et al. Sling surgery for stress urinary incontinence in women: a systematic review and metaanalysis. Am J Obstet Gynecol. 2014;210:1.e1–1.e27.)

Cure rates may be high, but complication rates are also higher with these procedures. These procedures are highly morbid, involve abdominal and transvaginal incisions, greater operative time, more blood loss, and more transfusions; autologous fascia has to be harvested from the patient using a separate incision; recovery time is much longer than other surgical treatment methods; and the complication rate is higher in terms of urinary retention, possible bone anchoring complications, hematoma, chronic pain, infection, exposure, and de novo urinary detrusor overactivity. (Chaikin DC, et al. Pubovaginal fascial sling for all types of stress urinary incontinence: long-term analysis. J Urol. 1998 Oct;160(4):1312–1316; Schimpf MO, et al. Sling surgery for stress urinary incontinence in women: a systematic review and metaanalysis. Am J Obstet Gynecol. 2014;210:1.e1–1.e27; Brubaker L. 5-Year Continence Rates, Satisfaction and Adverse Events of Burch Urethropexy and Fascial Sling Surgery for Urinary Incontinence. Urology. 2012;187:1324–1330; Richter HE, et al. Patient Related Factors Associated with Long-Term Urinary Continence After Burch Colposuspension and Pubovaginal Fascial Sling

Surgeries. Urology. 2012;188:485–489; Albo, ME, et al. Burch Colposuspension versus Fascial Sling to Reduce Urinary Stress Incontinence. N Engl J Med. 2007;356:2143–2155; Rehman H, et al. Traditional suburethral sling operations for urinary incontinence in women. Cochrane Database Syst Rev. 2011 Jan 19;(1):CD001754. doi: 10.1002/14651858.) In the SISTEr trial, 63% of the patients receiving fascial slings experienced adverse events. (Albo, ME, et al. Burch Colposuspension versus Fascial Sling to Reduce Urinary Stress Incontinence. N Engl J Med. 2007;356:2143–2155.) The AUA 2012 Update to the SUI Guidelines reported higher rates of pain and sexual dysfunction with pubovaginal slings than with midurethral slings. (Guideline for the Surgical Management of Female Stress Urinary Incontinence: 2009 Update Appendices A11 and A16.) Harvesting autologous fascia from the abdomen or outer thigh carries a risk of pain, nerve entrapment, and infection, which is a significant drawback to the procedure. The American College of Obstetricians and Gynecologists and the American Urogynecologic Society recommend that autologous fascial bladder neck slings be considered for women who decline or are not candidates for synthetic mesh slings. (ACOG / AUGS Practice Bulletin No. 155; Nov. 2015.) Using allografts and xenografts can be met with cultural or religious objections from patients, and carries a risk of disease transmission and rejection. Allografts and xenografts are also more costly than other materials, and lack the long-term durability of synthetic materials.

v. Midurethral Tension-Free Slings

Midurethral tension-free slings were developed by Ulmsten in Sweden in the 1980s to mid-1990s due to the high morbidity and unpredictable success of retropubic or proximal urethral suspension procedures. These procedures involve the placement of a tension-free synthetic midurethral sling that can be placed either retropubic or transobturator. They act as a hammock or backstop for the midurethra during the moments of increased bladder pressure caused by physical activity. Indications for midurethral slings are SUI with hypermobility of the urethra, SUI with ISD, mixed incontinence with stress predominance, and recurrent SUI following failed previous procedures. They have been used extensively in Europe for the treatment of SUI, became popular in the U.S. in the late 1990s, and have revolutionized the treatment of SUI. (Siddighi S, Hardesty JS. Urogynecology & Female Pelvic Reconstructive Surgery. ISBN 0-07-144799-7.) The majority are performed in ambulatory centers with minimal incision and without the requirement for post-operative catheterization. Other advantages are that it is a shorter learning curve for the surgeon (which means more women have access to the treatment), and they involve less post-operative pain for the patient. Most pelvic floor surgeons prefer synthetic midurethral slings to traditional procedures in most circumstances. (Clemons JL, et al. Impact of the 2011 FDA Transvaginal Mesh Safety Update on AUGS Members' Use of Synthetic Mesh and Biologic Grafts in Pelvic Reconstructive Surgery. Female Pelvic Med Reconstr Surg. 2013;19:191–198; Chughtai BI, et al. Midurethral Sling Is the Dominant Procedure for Female Stress Urinary Incontinence: Analysis of Case Logs From Certifying American Urologists. Urology. 2013 Dec;82(6):1267–71; Nager CW, et al. A Randomized Trial of Urodynamic Testing before Stress-Incontinence Surgery. N Engl J Med. 2012 May 24;366(21):1987–1997.)

IV. Ethicon TVT Products

a. Historical Background of Surgical Use of Mesh

Polypropylene sutures have been used for over 45 years and are biologically compatible with human tissue. Polypropylene hernia mesh has been and continues to be the standard of care for the last thirty years for abdominal wall hernia repair. Polypropylene mesh has been used in open abdominal sacrocolpopexies since the 1960s. The advantage of mesh is augmentation and strength during the healing process with the incorporation of collagen fibers into the material to provide lasting support. I have been performing polypropylene mesh hernia repairs since the 1980s and have never had a patient develop an infection or rejection of the material.

b. The Development of Tension-Free Vaginal Tape Using Prolene Mesh

As mentioned above, midurethral tension-free slings were developed by Ulmsten in Uppsala, Sweden in the 1980s to mid-1990s, at which time he and Dr. Petros experimented with multiple different available materials for the slings, including Mersilene, Marlex, Prolene, Gore-Tex, and others. (Petros PE. Creating a gold standard surgical device: scientific discoveries leading to TVT and beyond: Ulf Ulmsten Memorial Lecture 2014. Int Urogynecol J. 2015 Apr;26(4):471–6; Ulmsten U, et al. A multicenter study of tension-free vaginal tape (TVT) for surgical treatment of stress urinary incontinence. Int Urogynecol J Pelvic Floor Dysfunct. 1998;9(4):210–213; Petros PE, Ulmsten UI. An integral theory and its method for the diagnosis and management of female urinary incontinence. Scand J Urol Nephrol Suppl. 1993;153:1–93.) Dr. Ulmsten and Dr. Petros selected the monofilament, large-pore, knitted, lightweight Prolene mesh due to Prolene's long-term use in surgery as a suture material, its ease of use, and its biocompatibility in the vagina. Dr. Ulmsten also determined that a Prolene sling that was 1 centimeter in width and 40 centimeters in length was optimal. The width of the sling was eventually changed to 1.1 cm, and the length was subsequently increased to 45 cm to facilitate treatment of more women. Dr. Axel Arnaud of Ethicon went to Sweden in 1995 and observed four of Ulmsten's tension-free procedures and negotiated with Ulmsten to purchase the rights to the product he had developed. The TVT has been used extensively in Europe for the treatment of SUI and was introduced to the U.S. in 1998, becoming the gold standard for SUI surgery over the next several years.

c. The TVT, TVT-O, TVT-Exact, and TVT-Abbrevo Devices

The TVT is a monofilament, knitted, macroporous, lightweight, synthetic mesh sling that is swedged onto trocars that are passed at the midurethra via a 1.5 cm vaginal incision under the pubic symphysis and emanating approximately 2 cm lateral from the midline of the abdomen, just above the pubic symphysis. The mesh is encased in a plastic sheath that is removed after deployment of the mesh. The sling is not anchored; it is placed without tension under the mid-urethra, and a cough test is then performed to assess the degree of continence provided by the sling. The ends of the sling are cut beneath the surface of the skin on the abdominal wall after tensioning, and the vaginal incision is closed with an absorbable suture. Cystoscopy is performed to insure the bladder is not perforated by the sling during its deployment. The device comes in a box with the above-mentioned components, along with instructions for use for the

device. Internationally, the TVT is the most common midurethral synthetic sling that is utilized. The TVT has the longest studies available that have demonstrated both low complication rates and high efficacy, with studies carried out as long as 17 years. (Nilsson CG, et al. Seventeen years' follow-up of the tension-free vaginal tape procedure for female stress urinary incontinence. Int Urogynecol J. 2013 Aug;24(8):1265–1269. doi: 10.1007/s00192-013-2090-2.) The TVT is more cost effective, uses less operative time, and has a higher objective cure rate (at less than two years) than the laparoscopic Burch colposuspension. Compared to open Burch procedure, the TVT has a similar cure rate for up to two years of treatment, but is less costly and involves less recovery time. (Siddighi S, Hardesty JS. Urogynecology & Female Pelvic Reconstructive Surgery. ISBN 0-07-144799-7.)

The TVT-O, like the TVT, is a monofilament, knitted, macroporous, synthetic mesh sling that is swedged onto trocars that are passed at the midurethra via a 1.5 cm vaginal incision and through the obturator foramen and out the medial thigh. The same Prolene mesh is used in both the TVT and TVT-O slings. The mesh is a Type I mesh, per the biomaterial classification published by PK Amid in 1997, as it contains pores larger than 75 microns, "which is the required pore size for admission of macrophages, fibroblasts (fibroplasia), blood vessels (angiogenesis) and collagen fibers into the pores." (Amid PK. Classification of biomaterials and their related complications in abdominal wall hernia surgery. Hernia. 1997;1:15–21.) Like the TVT, the mesh of the TVT-O is encased in a plastic sheath that is removed after deployment of the mesh. The sling is not anchored; it is placed without tension, and a cough test is performed to assess the degree of continence provided by the sling. The ends of the sling are cut beneath the surface of the skin on the medial thigh after tensioning, and the vaginal incision is closed with an absorbable suture. It is recommended that cystoscopy be performed following the procedure, but I have found it to be optional due to the decreased likelihood of perforation of the bladder. The device comes in a box with the above-mentioned components along with instructions for use for the device. Hundreds of thousands of TVT-O procedures have been performed internationally since its introduction. It was first introduced in North America in 2004, and I performed the first case in North America in January 2004. The advantage of the transobturator approach is less risk of bladder perforation, retropubic hematoma, and possible bowel injury by avoiding the space of Retzius. The TVT-O procedure has a short learning curve, low morbidity, and a short operating time, and is technically simple to perform, which makes the procedure available to more women. (Groutz A, et al. Long-Term Outcome of Transobturator Tension-Free Vaginal Tape: Efficacy and Risk Factors for Surgical Failure. J Women's Health. 2010;20(10):1525–1528.) There are several long- or intermediate-term studies of the TVT-O supporting its safety and efficacy. (Groutz A, et al. Long-Term Outcome of Transobturator Tension-Free Vaginal Tape: Efficacy and Risk Factors for Surgical Failure. J of Women's Health. 2011;20(10):1525–1528; Laurikainen E, et al. Five-year Results of a Randomized Trial Comparing Retropubic and Transobturator Midurethral Slings for Stress Incontinence. Eur Urol. 2014 Jun;65(6):1109–14; Athanasiou S, et al. Seven years of objective and subjective outcomes of transobturator (TVT-O) vaginal tape: Why do tapes fail? Int Urogynecol J. 2014 Feb;25(2):219–225; Serati M, et al. TVT-O for the Treatment of Pure Urodynamic Stress Incontinence: Efficacy, Adverse Effects, and Prognostic Factors at 5-Year Follow-up. Eur Urol. 2013;63:872–78; Liapis A, et al. Efficacy of inside-out transobturator vaginal tape (TVTO) at 4 years follow up. Eur J Obstet Gynecol Reprod Biol. 2010 Feb;148(2):199–201; Angioli R, et al. Tension-Free Vaginal Tape Versus Transobturator Suburethral Tape: Five-Year Follow-up

Results of a Prospective, Randomised Trial. Eur Urol. 2010;58:671–677; Cheng D, et al. Tension-free vaginal tape-obturator in the treatment of stress urinary incontinence: a prospective study with five-year follow-up. Eur J Obstet Gynecol Reprod Biol. 2012;161:228–231.)

The TVT-Exact Continence System is a retropubic midurethral sling consisting of laser-cut Prolene polypropylene mesh that is 1.1 cm x 45 cm, covered by a clear plastic Implant Sheath and held between two white Trocar Sheaths that are bonded to the TVT-Exact implant and Implant Sheath. The mesh used in the TVT-Exact is the same lightweight, macroporous, monofilament mesh used in the TVT and TVT-O devices. The trocars of the TVT-Exact are thinner (3 mm v. 5 mm) and longer than the trocars of the TVT device. The device was launched in 2010. Thubert and colleagues published a retrospective study of 98 patients receiving either TVT or TVT-Exact who were followed for a minimum of one year. The authors found no significant difference in the rate of bladder injury. They also found less intense immediate post-operative pain in the TVT-Exact cohort, but by six weeks after surgery, the prevalence of pain ≥ 20/100 (VAS) no longer differed between the two groups. There was an increased post-void residual in the TVT-Exact group, but there was no between-group difference in post-operative self-catheterization, and the rate of tape release or cutting was also comparable in the two groups. The authors found a higher rate of post-operative bladder outlet obstruction symptoms in the TVT-Exact group, but there was no difference between the two groups when considering only de novo bladder outlet obstruction. The study showed that the prevalence of peri- and post-operative complications was equal in the two groups, and there was no significant difference in the success rate (no reported SUI and negative cough stress test). (Thubert T, et al. Bladder injury and success rates following retropubic mid-urethral sling: TVT EXACT vs. TVT. Eur J Obstet Gynecol Reprod Biol. 2016 Mar;198:78–83.)

The TVT-Abbrevo, like the TVT-O, is a transobturator midurethral sling consisting of laser-cut Prolene polypropylene mesh that is 1.1 cm x 12 cm, covered by clear polyethylene sheaths, and held between two Helical Passer Sheaths that are bonded to the mesh implant sheaths and the device's Positioning Lines, which are made of Prolene polypropylene monofilament suture. The device was developed by Professor Jean de Leval and Dr. David Waltregny. The mesh used in the TVT-Abbrevo is the same lightweight, macroporous, monofilament mesh used in the TVT and TVT-O devices. The device also comes with an Atraumatic Winged Guide, which is a stainless steel accessory that facilitates consistent passage of the TVT-Abbrevo implant through the dissection tract. It has a placement loop that aids the surgeon in centering the device. The device is implanted in a procedure involving reduced paraurethral dissection than the TVT-O procedure, with the obturator membrane being perforated only by the helical passer. The product was launched in 2010. There are several studies of the TVT-Abbrevo supporting its safety and efficacy and showing equal efficacy to the TVT-O, with low/equivalent complication rates and, in general, less pain in the early post-operative period.

In 2011, Dr. Piet Hinoul and colleagues published a cadaver study on an anatomic comparison of the TVT-O and a modified TVT-O that had only 12 cm of mesh (like the TVT-Abbrevo) rather than 45 cm, and found the modified device traversed fewer muscular structures, passed farther away from the obturator canal, the anterior obturator nerve, and the posterior obturator nerve, but the differences were not statistically significant. The modified device resulted in the implantation of significantly less mesh, while still consistently anchoring in the

obturator membrane. (Hinoul P, et al. An anatomic comparison of the original versus a modified inside-out transobturator procedure. Int Urogynecol J. 2011;22:997–1004.) Drs. Jean de Leval, Alexandre Thomas, and David Waltregny, also in 2011, published the one-year results of a prospective randomized controlled trial involving the TVT-O device and the same modified TVT-O device used in the aforementioned anatomic cadaver study. They studied 175 patients randomized to either the TVT-O (n=87) or modified TVT-O (n=88). There was no statistically significant difference in cure rates between the two groups (91.7% TVT-O and 90.7% modified TVT-O), but they found an increase in the incidence and intensity of groin pain in the original TVT-O group on day 0 and 1, but not thereafter. One patient receiving a TVT-O had a suburethral vaginal exposure requiring partial tape excision, but there were no exposures in the modified TVT-O group. (de Leval J, et al. The original versus a modified inside-out transobturator procedure: 1-year results of a prospective randomized trial. Int Urogynecol J. 2011;22:145–56.)

Drs. Waltregny and de Leval published three-year data on their randomized controlled trial involving the TVT-O versus TVT-Abbrevo in 2012. 87% of the patients completed the 3-year follow-up, and an 84.3% subjective cure rate was seen overall, with no statistically significant difference between the two groups. 85.7% of the TVT-O patients and 87.7% of the TVT-Abbrevo patients had a negative cough test at the 3-year follow-up ($p>0.05$). 1 patient (1.3%) in the TVT-O group and 3 patients (4.1%) in the TVT-Abbrevo group reported thigh pain at three years, but did not complain about the pain and had a pain score of ≤ 3. (Waltregny D, de Leval J. New Surgical Technique for Treatment of Stress Urinary Incontinence—TVT-ABBREVO: From Development to Clinical Experience. Surg Technol Int. 2012 Dec;22:149–57.) Dr. Giovanni A. Tommaselli and colleagues published their single-blind randomized study of the TVT-O and TVT-Abbrevo in 2012. They studied 72 patients randomized to either the TVT-O procedure or the TVT-Abbrevo procedure and evaluated post-operative pain, objective cure rate, and quality-of-life scores. They found that pain scores were significantly lower in the TVT-Abbrevo group at 24 hours after the surgery, but they did not find any significant difference in the number of analgesic vials administered, cure rates, and questionnaire scores between the two groups. At one month after surgery, there was no significant difference between the VAS pain scores in the groups. (Tommaselli GA, et al. Effects of a modified technique for TVT-O positioning on postoperative pain: single-blind randomized study. Int Urogynecol J. 2012;23:1293–99.) Dati and colleagues conducted a randomized controlled trial involving patients treated with TVT-Abbrevo or the Ajust Mini-Sling, and found higher cure rates in the TVT-Abbrevo patients. (Dati S, et al. Single-Incision Minisling (Ajust) vs. Obturator Tension-Free Vaginal Shortened Tape (TVT_Abbrevo) in Surgical Management of Female Stress Urinary Incontinence. Int J Gynecol & Obstet. 2012;119S3:S531–S867, Abs. M432.)

Narang and colleagues conducted a study of 56 patients who were treated with the TVT-Abbrevo. The authors found that at one month, 98% of patients were subjectively cured of SUI, and that 89.3% were subjectively cured at 6 months. Objective cure based on urodynamic testing was 88.8% at 6 months. At 1 month, 1 patient had pain, and the mean pain score was 0.04 ± 0.28. At 6 months and 1 year, no patients had pain. There was one patient who developed a tape erosion in the vagina at 6 months, and 1 patient who developed recurrent UTIs over 6 months. (Narang S, Han HC. Initial Experience of TVT-Abbrevo at a Tertiary Care Hospital. ICS Abs. 682, 2013.) In 2014, Capobianco and colleagues published the results of a

study of 56 women treated with the TVT-Abbrevo with 2-year follow-up. The authors found that 76.79% of patients were subjectively cured at 1 year, with an additional 17.86% of patients experiencing considerable improvement in symptoms. There was only 1 case of de novo OAB. There were no cases of vaginal erosion at follow-up visit, and no cases of persistent groin pain at long-term follow-up. The authors concluded that the TVT-Abbrevo provides "high objective and subjective long term efficacy, a clinically meaningful improvement in patient quality of life, and an excellent safety profile." They found the positioning of the TVT-Abbrevo to be technically simple, and found it very easy to position the tape lying flat under the urethra. (Capobianco G, et al. TVT-ABBREVO: efficacy and two years follow-up for the treatment of stress urinary incontinence. Clin Exp Obstet Gynecol. 2014;41(4):445–7.)

In 2014, Kurien and colleagues reported on a prospective cohort study of the efficacy and safety of the TVT-Abbrevo with a maximum of 22-month follow-up and found a subjective cure rate of 94.6% at 1 year and an objective cure rate of 86.7% at 6 months. Seventy-nine percent of the patients were relieved of their urgency and urge incontinence, and 8.3% had an improvement of their OAB symptoms at one year. There were no bladder perforations and only 2 vaginal perforations. Only 7 of the 76 patients had any pain at the first follow-up on day 3–10, but none of the 7 had a VAS score of greater than 5. Persistent pain needing any kind of analgesia was 0% at 1 month, 6 months, and 1 year. Only 2 of the 76 patients experienced a vaginal tape erosion, and they were asymptomatic. There were no recurrent urinary tract infections at one year, and de novo OAB symptoms were noted in only 1 patient at 1-year follow-up. (Kurien A, et al. TVT Abbrevo for management of female stress urinary incontinence: a prospective analysis over 22 months in a tertiary care hospital. Br J Obstet Gynecol. 2014 Jan;121(2):235–236 EP13.17.) In 2015, Shaw and colleagues reported the results of their retrospective cohort study of all women undergoing treatment with a TVT-O or a TVT-Abbrevo. The authors found that only 1 patient in the TVT-Abbrevo group experienced bothersome groin pain, and concluded that use of the TVT-Abbrevo reduces post-operative groin pain compared to the TVT-O without any reduction in efficacy. (Shaw JS, et al. Decreasing transobturator sling groin pain without decreasing efficacy using TVT-Abbrevo. Int Urogynecol J. 2015 Sep;26(9):1369–72.)

Canel and colleagues published a retrospective study comparing 50 patients treated with the TVT-Abbrevo to 50 patients treated with the TVT-O. They found there to be less post-operative pain in the TVT-Abbrevo group than in the TVT-O group, but at 6 weeks after surgery, there was no statistically significant difference between the two groups of patients. There was no statistically significant difference in the rate of de novo bladder outlet obstruction symptoms, and the rate of peri- and post-operative complications were equal in the two groups. Success rates between the groups were also similar at 12 months after surgery. (Canel V, et al. Postoperative groin pain and success rates following transobturator midurethral sling placement: TVT ABBREVO® system versus TVT™ obturator system. Int Urogynecol J. 2015 Oct;26(1):1509–16.)

In 2016, Tommaselli and colleagues published a retrospective study looking at cure rates and complications in overweight and normal-weight women undergoing the TVT-Abbrevo procedure. The authors found no statistically significant difference in objective or subjective cure rates at 12-month follow-up. There were no serious intra-operative or post-operative complications observed, and there were no differences in pain visual analogue scores or the

number of analgesic vials administered in the two groups of women. (Tommaselli GA, et al. Efficacy and safety of the trans-obturator TVT-Abbrevo device in normal weight compared to overweight patients affected by stress urinary incontinence. Eur J Obstet Gynecol Reprod Biol. 2016 Feb;197:116–9.)

A recent high-quality Cochrane meta-analysis review of the literature concludes that midurethral slings like the TVT, TVT-O, TVT-Abbrevo, and TVT-Exact have similar efficacy to the Burch procedure, but the midurethral sling procedures involve shorter recovery time. The review further concludes that midurethral synthetic sling operations are the most extensively researched surgical treatment for SUI in women and have a good safety profile. The TVT, in particular, is the most studied mesh device, with more than 100 randomized controlled trials having been done with the device. The mesh used in the TVT, TVT-O, TVT-Abbrevo, and TVT-Exact is the most studied of any of the meshes used in stress incontinence surgery. The Cochrane review authors note that irrespective of the routes traversed, synthetic mesh midurethral slings are highly effective in the short- and medium-term, and evidence demonstrates their effectiveness in the long-term. The Cochrane Review illustrates positive impact on improving the quality of life of women with SUI. With the exception of groin pain, fewer adverse events occur with employment of a transobturator approach. (Ford AA, Rogerson L, Cody JD, Ogah J. Mid-urethral sling operations for stress urinary incontinence in women. Cochrane Database Syst Rev. 2015, Issue 7. Art. No.: CD006375. doi: 10.1002/ 14651858.CD006375.pub3.) The 2015 Cochrane systematic review demonstrates that both retropubic and transobturator approaches appear to be comparable in terms of efficacy and patient satisfaction. (ACOG / AUGS Practice Bulletin No. 155; Nov. 2015.) However, a 2015 systematic review and meta-analysis observed similar rates of objective cure between transobturator and retropubic midurethral slings, and higher subjective cure rates in retropubic slings. (Tommaselli GA, et al. Medium-term and long-term outcomes following placement of midurethral slings for stress urinary incontinence: a systematic review and metaanalysis. Int Urogynecol J. 2015 Sep;26(9):1253–68. doi: 10.1007/s00192-015-2645-5.)

In 2010, Novara added 14 new trials to their 2007 systematic review metaanalysis evaluating efficacy, complication rate, and reoperation rate of Burch colposuspension and synthetic midurethral slings. Midurethral slings were found to have higher objective cure rates than Burch colposuspension. Similar rates of postoperative complications, including pelvic hematoma, UTI, postoperative lower urinary tract symptoms, and reoperation were noted between the two groups. Midurethral slings resulted in a greater improvement in patient quality of life over the Burch procedure in two trials. Midurethral slings were also found to be more cost-effective than the Burch procedure. (Cox A, Herschorn S, Lee L. Surgical management of female SUI: is there a gold standard? Nat Rev Urol. 2013 Feb;10(2):78–89. doi: 10.1038/ nrurol.2012.243. Erratum: Nat Rev Urol. 2013 Apr;10(4):188.) Based on the literature, a new gold standard for first-line surgical treatment for women with SUI has emerged—the synthetic midurethral sling inserted via retropubic or transobturator approach. (Cox A, Herschorn S, Lee L. Surgical management of female SUI: is there a gold standard? Nat Rev Urol. 2013 Feb;10(2):78–89. doi: 10.1038/nrurol.2012.243. Erratum: Nat Rev Urol. 2013 Apr;10(4):188.) Studies have shown that midurethral slings are superior to both the Burch procedure and pubovaginal slings in terms of cure rates. (Schimpf MO, et al. Sling surgery for stress urinary incontinence in women: a systematic review and metaanalysis. Am J Obstet Gynecol.

2014;210:1.e1–1.e27.) Objective cure rate at one year is greater than 90%, and 85% at seventeen years. (Nilsson CG, et al. Seventeen years' follow-up of the tension-free vaginal tape procedure for female stress urinary incontinence. Int Urogynecol J. 2013 Aug;24(8):1265–1269. doi: 10.1007/s00192-013-2090-2.)

Due to the increased morbidity of the open Burch procedure, it is less frequently taught in residencies and fellowships. Almost all residents, however, are trained on midurethral slings as the primary treatment option for SUI management. The TVT retropubic and transobturator approaches are commonly taught and performed in training programs throughout the world.

The TVT and TVT-O have proven long-term efficacy due to the permanence and stability of the mesh and are superior in efficacy to retropubic suspensions. (Aigmueller T, et al. Ten-year follow-up after the tension-free vaginal tape procedure. Am J Obstet Gynecol. 2011 Nov;205(5):496.e1–5.) Compared with open or laparoscopic colposuspension the success rates are more stable with a lesser decline of success over years. Reported long-term success rates after open or laparoscopic colposuspension vary between 36% and 69%. (Alcalay M, et al. Burch colposuspension: a 10–20 year follow up. Br J Obstet Gynaecol. 1995;102:740–745; Barr S. The long-term outcome of laparoscopic colposuspension: a 10-year cohort study. Int Urogynecol J Pelvic Floor Dysfunct. 2009 Apr:20(4):443–5. doi: 10.1007/s00192-008-0798-1.)

I have personally performed over 1,000 TVT procedures, including the TVT, the TVT-O and the more recent TVT-Exact and TVT-Abbrevo, and have found the products to be safe and efficacious when following the appropriate patient selection and the technique described by Drs. Ulmsten and de Leval, which is covered in the product instructions for use. I have lectured and proctored physicians on the safe use of the TVT, TVT-O, and several other devices since 2000. The devices are high quality, straightforward, and the polypropylene mesh is stable over time, as I have patients implanted 15 years ago and see no long-term complication trends. Since the television advertisements claiming pelvic mesh is a dangerous product, I have received hundreds of phone calls from anxious patients with fears of product recalls and future complications. The overwhelming majority of those anxious patients have excellent outcomes and no adverse symptoms. The effect on current patients is to create fear that a synthetic sling will cause future problems and many choose not to proceed to treatment. There is a 30% reduction in the number of patients undergoing stress incontinence and pelvic reconstructive surgery. (Perkins CE, Warrior K, Eilber KS, et al. The Role of Mid-urethral Slings in 2014: Analysis of the Impact of Litigation on Practice. Curr Bladder Dysfunct Rep. (2015) 10:39–45. doi: 10.1007/s11884-014-0278-z; Koo K, Gormley EA. Abstract MP81-05: Transvaginal Mesh in the Media Following the 2011 FDA Update.)

The efficacy and safety of the TVT-O, TVT-Abbrevo, and the retropubic TVT slings are well-reported. The TVT is the most studied midurethral sling, with more than 100 RCTs. The TVT-O has also been extensively studied—with thousands of patients included in the collection of studies. Additionally, the following professional organization position statements and guidelines and FDA publications have addressed the safety, efficacy, and widespread acceptance of synthetic mesh midurethral slings like the TVT and TVT-O.

- **ACOG / AUGS Practice Bulletin No. 155 (Nov. 2015)**
  - "Synthetic midurethral mesh slings are the most common primary surgical treatment for stress urinary incontinence in women. Synthetic midurethral slings demonstrate efficacy that is similar to traditional suburethral fascial slings, open colposuspension, and laparoscopic colposuspension. Compared with suburethral fascial slings, fewer adverse events have been reported with synthetic midurethral slings. Voiding dysfunction is more common with open colposuspension than with synthetic midurethral slings. For these reasons, midurethral synthetic mesh slings have become the primary surgical treatment for stress urinary incontinence in women."
  - "Although controversy exists about the role of synthetic mesh used in the vaginal repair of pelvic organ prolapse, there are substantial safety and efficacy data that support the role of synthetic mesh midurethral slings as a primary surgical treatment option for stress urinary incontinence in women. For this reason, and to clarify uncertainty for patients and practitioners, the American Urogynecologic Society and the Society of Urodynamics, Female Pelvic Medicine & Urogenital Reconstruction published a position statement recognizing polypropylene mesh midurethral slings as the 'standard of care' in the surgical treatment of stress urinary incontinence."
- **AUGS-SUFU, Position Statement on Mesh Midurethral Slings for Stress Urinary Incontinence (Jan. 3, 2014) (updated June 2016 and supported by the American Association of Gynecological Laparoscopists, the American College of Obstetricians and Gynecologists, the National Association for Continence, the Society of Gynecologic Surgeons, and the Women's Health Foundation)**
  - "Polypropylene material is safe and effective as a surgical implant. Polypropylene has been used in most surgical specialties (including general surgery, cardiovascular surgery, transplant surgery, ophthalmology, otolaryngology, gynecology, and urology) for over five decades, in millions of patients in the US and the world (personal communication with manufacturers of polypropylene suture and mesh)."
  - "As a knitted implant for the surgical treatment of SUI, macroporous, monofilament, light weight polypropylene has demonstrated long term durability, safety, and efficacy up to 17 years."
  - "The monofilament polypropylene mesh MUS is the most extensively studied anti-incontinence procedure in history. A broad evidence base including high quality scientific papers in medical journals in the US and the world supports the use of the MUS as a treatment for SUI. There are greater than 2000 publications in the scientific literature describing the MUS in the treatment of SUI. These studies include the highest level of scientific evidence in the peer reviewed scientific literature. . . . No other surgical treatment for SUI before or since has been subject to such extensive investigation."
  - "Polypropylene mesh midurethral slings are the standard of care for the surgical treatment of SUI and represent a great advance in the treatment of

this condition for our patients. Since the publication of numerous level one randomized comparative trials, the MUS has become the most common surgical procedure for the treatment of SUI in the US and the developed world. This procedure has essentially replaced open and transvaginal suspension surgeries for uncomplicated SUI. . . . Full-length midurethral slings, both retropubic and transobturator, have been extensively studied, are safe and effective relative to other treatment options and remain the leading treatment option and current gold standard for stress incontinence surgery. Over 3 million MUS have been placed worldwide and a recent survey indicates that these procedures are used by > 99% of AUGS members."

- "The polypropylene midurethral sling has helped millions of women with SUI regain control of their lives by undergoing a simple outpatient procedure that allows them to return to daily life very quickly. With its acknowledged safety and efficacy it has created an environment for a much larger number of women to have access to treatment. In the past, concerns over failure and invasiveness of surgery caused a substantial percent of incontinent women to live without treatment. One of the unintended consequences of this polypropylene mesh controversy has been to keep women from receiving any treatment for SUI. This procedure is probably the most important advancement in the treatment of stress urinary incontinence in the last 50 years and has the full support of our organizations which are dedicated to improving the lives of women with urinary incontinence."

- **AUGS Position Statement on Restriction of Surgical Options for Pelvic Floor Disorders (2013)**
  - "The American Urogynecologic Society strongly opposes any restrictions by state or local medical organizations, healthcare systems, or insurance companies which ban currently available surgical options performed by qualified and credentialed surgeons on appropriately informed patients with pelvic floor disorders."
  - "In a recent study involving 53 expert urologists and urogynecologists (of whom > 90% were fellowship trained) and who could select among many surgical options, the full-length synthetic midurethral sling was the preferred option in 93% for the surgical treatment of primary stress incontinence. Full-length midurethral slings, both retropubic and transobturator, have been extensively studied, are safe and effective relative to other treatment options and remain the leading treatment option and current gold standard of care for stress incontinence surgery."
- **AUA Position Statement on the Use of Vaginal Mesh for the Surgical Treatment of Stress Urinary Incontinence (Nov. 2011)**
  - "Suburethral synthetic polypropylene mesh sling placement is the most common surgery currently performed for SUI. Extensive data exist to support the use of synthetic polypropylene mesh suburethral slings for the treatment of female SUI, with minimal morbidity compared with alternative surgeries. Advantages include shorter operative

time/anesthetic need, reduced surgical pain, reduced hospitalization, and reduced voiding dysfunction. Mesh-related complications can occur following polypropylene sling placement, but the rate of these complications is acceptably low."

- "Multiple case series and randomized controlled trials attest to the efficacy of synthetic polypropylene mesh slings at 5–10 years. This efficacy is equivalent or superior to other surgical techniques. There is no significant increase in adverse events observed over this period of follow-up. Based on these data, the AUA Guideline for the Surgical Management of Stress Urinary Incontinence (2009) concluded that synthetic slings are an appropriate treatment choice for women with stress incontinence, with similar efficacy but less morbidity than conventional non-mesh sling techniques."

- **IUGA – Stress Urinary Incontinence – A Guide for Women (2011)**
  - "Before 1993, the treatment of stress incontinence often involved major surgery with an abdominal incision. The most common treatment now involves the use of a permanent sling that lies under the middle section of the urethra."
- **ICS Fact Sheets: A Background to Urinary and Faecal Incontinence (July 2013)**
  - "Worldwide, midurethral slings comprised of synthetic mesh have become the treatment of choice for SUI. Long-term data are robust and demonstrate durable efficacy with a very low complication rate, particularly in experienced hands. Various techniques for sling placement and different meshes are employed according to physician preference, but all appear to be equally effective."
- **Lucas MG, Ruud JLB, Burkhard FC, et al. EAU Guidelines on Surgical Treatment of Urinary Incontinence. Eur Urol. 2012 Dec;62(6):1118–1129.**
  - "There has been a rapid adoption of midurethral synthetic sling insertion as the first-line surgical option for SUI because it is effective, it is less invasive, and patients recover more quickly."
  - Notes that a systematic review of midurethral slings with both open colposuspension and laparoscopic colposuspension showed that retropubic insertion of a synthetic midurethral sling gave equivalent patient-reported and superior clinician-reported cure of SUI compared with colposuspension at 12 months; transobturator insertion gave equivalent patient-reported and clinician-reported cure of SUI at 12 months. Also notes that midurethral sling insertion was associated with a lower rate of new symptoms of urgency and voiding dysfunction compared with colposuspension.
- **NICE clinical guideline 171. Urinary incontinence: The management of urinary incontinence in women. (Sept. 2013)**
  - Notes that if conservative management for SUI has failed, the surgeon should offer, among other options, a synthetic midurethral tape.
  - Notes that, when offering a synthetic midurethral tape procedure, surgeons should use procedures and devices for which there is current high quality

evidence of efficacy and safety. Footnote 11 then notes that at the time of publication, TVT and TVT-O (among others) met this guideline.

- **FDA, Considerations about Surgical Mesh for SUI (2013)**
  - "Mesh sling procedures are currently the most common type of surgery performed to correct SUI. Based on industry estimates, there were approximately 250,000 of these procedures performed in 2010."
  - "The safety and effectiveness of multi-incision slings is well-established in clinical trials that followed patients for up to one-year. Longer follow-up data is available in the literature, but there are fewer of these long-term studies compared to studies with one-year follow-up."
- **FDA Executive Summary, Surgical Mesh for Treatment of Women with Pelvic Organ Prolapse and Stress Urinary Incontinence (Sept. 8–9, 2011)**
  - Notes that the Burch has a long history, but its popularity has declined over the past two decades with the introduction of less invasive procedures. Notes that pubovaginal sling procedures using biologic graft material (often autologous fascia) similarly have declined in popularity.
  - Notes that anterior repair with Kelly plication to correct SUI in the presence of a cystocele and bladder neck needle suspension is rarely performed currently due to poor long-term outcomes.
  - "A substantial number of quality clinical trials, as well as systematic reviews, have been published for the first generation minimally invasive slings that provide evidence of safety and effectiveness of these devices." (p. 28).
  - "After considering all available data on both safety and effectiveness, and considering the risk/benefit profile, it appears that new premarket clinical trials are not warranted for minimally invasive slings for SUI unless the device has new features (*e.g.* new polymer or coating) that could affect device performance."
- **FDA 24-hr Summary – Ob/Gyn Devices Panel (Sept. 8–9, 2011)**
  - Notes that the panel consensus on retropubic and transobturator suburethral slings was that the "safety and effectiveness of these devices is well-established."
- **Dmochowski RR, Blaivas JM, Gormley EA, et al. Update of AUA Guideline on the Surgical Management of Female Stress Urinary Incontinence. J Urol. 2010 May;183(5):1906–1914.**
  - Noting the importance of the transobturator technique in the treatment of SUI and that midurethral slings are one treatment modality that may be considered for the index patient.
- **AUA Position Statement on the Use of Vaginal Mesh for the Surgical Treatment of Stress Urinary Incontinence (2012)**
  - "Suburethral synthetic polypropylene mesh sling placement is the most common surgery currently performed for SUI. Extensive data exist to support the use of synthetic polypropylene mesh suburethral slings for the treatment of female SUI, with minimal morbidity compared with alternative surgeries. Advantages include shorter operative time/anesthetic need, reduced surgical pain, reduced hospitalization, and

reduced voiding dysfunction. Mesh-related complications can occur following polypropylene sling placement, but the rate of these complications is acceptably low. Furthermore, it is important to recognize that many sling-related complications are not unique to mesh surgeries and are known to occur with non-mesh sling procedures as well. It is the AUA's opinion that any restriction of the use of synthetic polypropylene mesh suburethral slings would be a disservice to women who choose surgical correction of SUI."

- "Multiple case series and randomized controlled trials attest to the efficacy of synthetic polypropylene mesh slings at 5–10 years. This efficacy is equivalent or superior to other surgical techniques. There is no significant increase in adverse events observed over this period of follow-up. Based on these data, the AUA Guideline for the Surgical Management of Stress Urinary Incontinence (2009) concluded that synthetic slings are an appropriate treatment choice for women with stress incontinence, with similar efficacy but less morbidity than conventional non-mesh sling techniques."

Plaintiffs' experts' theory of mesh degradation is not substantiated in the literature or in my personal experience using polypropylene slings and mesh for incontinence treatment and pelvic reconstruction. Studies of explanted mesh are difficult to interpret, as there is damage to the material during explantation, treatment with chemicals to remove the collagen and biologic matrix that has incorporated into the mesh, and preparation onto slides for microscopic examination. There is no literature to support clinically significant mesh degradation in humans. Polypropylene suture is used by vascular surgeons on major blood vessels, and in my practice, when tying off renal arteries and repairing the largest vein in the body; the vena cava. If there was a question of degradation or loss of strength over time, Prolene suture would not be the suture of choice for the highest-risk surgery. The studies often relied on by plaintiffs' experts, offering the opinion that the Prolene mesh degrades, are unreliable and do not support that theory. For instance, the Clavé study from 2010 is unreliable and does not show degradation. The chemical analyses performed on a limited subset of the specimens does not show degradation, and the scanning electron microscope photos in the study show surface cracking that could be from biologic material and handling or preservation rather than the cracking of the polypropylene itself. Also, the sample analyzed in the study was only 32 out of the 100 specimens, and the authors fail to discuss how those 32 specimens were selected. They also fail to discuss whether the mesh was damaged during surgical explantation. Other literature indicates that cracking seen on the surface of explanted Prolene or polypropylene is not degraded Prolene or polypropylene, but rather a cracked biofilm. (de Tayrac R and Letouzey V, Basic science and clinical aspects of mesh infection in pelvic floor reconstructive surgery, Int Urogynecol J. 2011 Jul;22(7):775-80; Ong KL, White J, and Thames SF, The Myth: In Vivo Degradation of Polypropylene Meshes, IUGA Abs. PP 19, 2016.)

Nor have I seen a problem with Prolene mesh roping or curling, unless it is placed improperly by over-tensioning. Nor have I observed particle loss from mechanically cut mesh in my practice. Even if there were particle loss from the mechanically cut Prolene mesh, the particles lost would be the same Prolene as the suture material that is FDA approved as safe and

effective for use in the human body. Furthermore, the mesh does not contract or experience pore collapse when placed according to the IFU. The sheath that covers the mesh on the TVT, TVT-O, TVT-Abbrevo, and TVT-Exact devices protects the tissue against trauma, helps the mesh pass through the tissue smoothly, and carries the forces of implantation so that the mesh retains its shape. Scar tissue that forms after any pelvic surgery contracts, and tissue incorporating into implanted mesh is no exception, but the mesh itself does not contract. (Nilsson, CG. Seventeen years' follow-up of the tension-free vaginal tape procedure for female stress urinary incontinence. Int Urogynecol J. 2013 Aug;24(8):1265–1269; Lukacz ES, et al. The effects of the tension-free vaginal tape on proximal urethral position: a prospective, longitudinal evaluation. Int Urogynecol J Pelvic Floor Dysfunct. 2004 Jan–Feb;15(1):32–38; discussion 38.)

There is no practical or clinical difference between mechanically cut or laser-cut mesh in terms of how it is deployed or incorporated in the tissues. (ETH.MESH.01784823–28 (CER Laser Cut Mesh); ETH.MESH.01222075–79 (Elongation Characteristics of Laser Cut Prolene Mesh for TVT); ETH.MESH.06696367–79 (Performance Evaluation of TVT U Prolene Mesh); Lin AT, et al. In Vivo tension Sustained by Fascial Sling in Pubovaginal Sling Surgery for Female Stress Urinary Incontinence. J Urol. 2005 Mar;173(3):894–897.) Mesh is not pre-stretched to 50% elongation before it is used, and it is implanted with trocars and with a protective sheath over the mesh. The mesh sling must be stiff enough to lie flat against the posterior urethra with porosity large enough to encourage fibroblast and collagen deposition for incorporation, and it must have enough elasticity to allow give during dynamic stressing that occurs with activity. Mesh requires an optimal level of stiffness to properly do its job supporting the urethra. Based on my experience and my assessment of the available literature, I do not believe that any particle loss from mechanically cut Prolene polypropylene mesh has a clinical effect in patients. Both laser-cut and mechanically cut Prolene mesh is safe and efficacious as demonstrated by the medical literature and in my experience.

Plaintiffs' experts assert that the Prolene mesh used in the TVT, TVT-O, TVT-Abbrevo, and TVT-Exact devices is small-pore mesh. That is not true. The Ethicon TVT mesh has the largest porosity, and greatest elasticity of all the SUI meshes available. It is also monofilament and knitted to provide the optimal combination of biocompatibility and minimal inflammatory response. The mesh—which has a pore size of approximately 1,379 microns—allows adequate tissue incorporation/ingrowth. (Amid PK. Classification of biomaterials and their related complications in abdominal wall hernia surgery. Hernia. 1997;1(1):15–21.) The Ethicon mesh is not associated with an increased risk of infection compared to other SUI vaginal surgeries. Verified infection after TVT, TVT-O, TVT-Abbrevo, or TVT-Exact is a very rare occurrence, and has not occurred in my practice in over 1,000 cases and 15 years.

Nor is the mesh in the TVT, TVT-O, TVT-Abbrevo, or TVT-Exact devices "heavyweight" mesh. Synthetic slings require an optimal amount of weight/density to properly do their job supporting the urethra without adversely affecting its function. Indeed, seventeen-year follow-up substantiates the biocompatibility of the weight/stiffness/elasticity and porosity of the TVT mesh. At seventeen years of follow-up, 91.3% of patients' SUI was objectively cured, and there was no tape rejection, no clinically significant contracture, and only one mesh exposure, which was not symptomatic and was due to vaginal atrophy in an elderly patient.

(Nilsson, CG. Seventeen years' follow-up of the tension-free vaginal tape procedure for female stress urinary incontinence. Int Urogynecol J. 2013 Aug;24(8):1265–1269.)

Plaintiffs' experts have also claimed that the mesh used in the TVT, TVT-O, TVT-Abbrevo, and TVT-Exact devices is cytotoxic and causes an excessive inflammatory response. This is not supported in the literature, and I have not seen it in my practice. The long-term studies on the TVT and TVT-O mesh belie this claim. Studies show minimal inflammation associated with the Prolene mesh used in TVT and TVT-O, and practically no tissue reaction out to two years. (Falconer C, et al. Influence of different sling materials on connective tissue metabolism in stress urinary incontinent women. Int Urogynecol J Pelvic Floor Dysfunct. 2001;12 Suppl 2:S19–23.) The mere presence of chronic inflammatory cells in a tissue specimen does not prove that there is a chronic inflammatory process that is active. Such cells can be present but quiescent, and can be seen in vaginal tissue even when no mesh or other foreign body has been implanted. If it were the case that the mesh in the TVT, TVT-O, TVT-Abbrevo, and TVT-Exact devices was cytotoxic, the many intermediate- and long-term studies on the TVT and TVT-O devices would not demonstrate the high efficacy and low complication rates that they do.

Any suggestion by plaintiffs' experts that PVDF is a safer alternative to the Prolene mesh used in the TVT, TVT-O, TVT-Abbrevo, and TVT-Exact devices is untenable. There is no mid- or long-term data supporting the use of PVDF in SUI treatment. To my knowledge, PVDF has not been studied to treat SUI in women. Plaintiffs' experts may also claim that Ultrapro or Vypro mesh would have been a safer alternative to the Prolene mesh used in the TVT and TVT-O slings. However, with respect to Vypro, a study of the use of that mesh in pelvic floor surgery showed that tolerance of the Vypro mesh was "very poor" and associated with high rates of erosion and cicatrisation. (Denis S, et al. Pelvic Organ Prolapse Treatment by the Vaginal Route Using a Vypro Composite Mesh: Preliminary Results About 106 Cases. ICS IUGA 2004; Abstract 620.) With respect to Ultrapro, the study often cited by plaintiffs' experts in support of that material as a safer alternative to the Prolene TVT mesh is the Okulu study, but that study does not compare TVT mesh to Ultrapro mesh, and involves a technique completely different than the one used to implant the TVT or TVT-O slings. (Okulu E, et al. Use of three types of synthetic mesh material in sling surgery: A prospective randomized clinical trial evaluating effectiveness and complications. Scand J Urol. 2013 Jun;47(3):217–224.) Ethicon studied the use of Ultrapro mesh with a sheath and found that the force required to remove the sheath was excessive, which it believed to be due to the fact that the mesh stuck to the sheath after sterilization. (R&D Memorandum on PA Mesh Assessments for TVTO-PA, ETH.MESH.09922570.)

Plaintiffs' experts sometimes suggest or claim that the Prolene mesh is carcinogenic, but there is no reliable scientific evidence to support the theory or claim that polypropylene can cause cancer or sarcoma. In the more than 1,000 cases in which I have implanted one of the TVT family of products, I have not seen a single case of cancer attributable to the mesh. The literature also refutes plaintiffs' experts' suggestion or claim. (King AB, et al. Is there an association between polypropylene midurethral slings and malignancy? Urology. 2014 Oct;84(4):789–92; King AB, Goldman HB. Current controversies regarding oncologic risk associated with polypropylene midurethral slings. Curr Urol Rep. 2014 Nov;15(11):453; Linder BJ, et al. Evaluation of the local carcinogenic potential of mesh used in the treatment of female

stress urinary incontinence. Int Urogynecol J. 2016 Feb 10. doi: 10.1007/s00192-016-2961-4.) The medical literature contains no case reports of tumors caused by or associated with polypropylene implantation despite the fact that polypropylene has been implanted in millions of people. (AUGS & SUFU. Frequently Asked Questions by Providers—Mid-urethral Slings for Stress Urinary Incontinence (Mar. 12, 2014) (available at http://www.augs.org/p/bl/et/blogaid=194).)

The mesh used in the TVT, TVT-O, TVT-Abbrevo, and TVT-Exact slings is the most commonly used mesh for treatment of stress urinary incontinence and is state of the art. Many long- and intermediate-term studies consistently show that the TVT and TVT-O—and the mesh used in those devices as well as in the TVT-Abbrevo and TVT-Exact devices—are safe and effective and the standard of care for surgical treatment of SUI. (Serati M, et al. TVT for the Treatment of Urodynamic Stress Incontinence: Efficacy and Adverse Effects at 13-Year Follow-Up. Neurourol and Urodyn. 2015 Oct 19. doi: 10.1002/nau.22914; Groutz A, et al. Long-Term Outcome of Transobturator Tension-Free Vaginal Tape: Efficacy and Risk Factors for Surgical Failure. J Womens Health (Larchmt). 2011 Oct;20(10):1525–1528; Laurikainen E, et al., Five-year Results of a Randomized Trial Comparing Retropubic and Transobturator Midurethral Slings for Stress Incontinence. Eur Urol. 2014 Jun;65(6):1109–14; Athanasiou S, et al. Seven years of objective and subjective outcomes of transobturator (TVT-O) vaginal tape: Why do tapes fail? Int Urogynecol J. 2014 Feb;25(2):219–225; Serati M, et al. TVT-O for the Treatment of Pure Urodynamic Stress Incontinence: Efficacy, Adverse Effects, and Prognostic Factors at 5-Year Follow-up. Eur Urol. 2013 May;63(5):872–78; Liapis A, et al. Efficacy of inside-out transobturator vaginal tape (TVTO) at 4 years follow up. Eur J Obstet Gynecol Reprod Biol. 2010 Feb;148(2):199–201; Angioli R, et al. Tension-Free Vaginal Tape Versus Transobturator Suburethral Tape: Five-Year Follow-up Results of a Prospective, Randomised Trial. Eur Urol. 2010 Nov;58(5):671–677; Cheng D, Liu C. Tension-free vaginal tape-obturator in the treatment of stress urinary incontinence: a prospective study with five-year follow-up. Eur J Obstet Gynecol Reprod Biol. 2012 Apr;161(2):228–231; Heinonen P, et al. Tension-free vaginal tape procedure without preoperative urodynamic examination: long-term outcome. Int J Urol. 2012 Nov;19(11):1003–9; Aigmueller T, et al. Ten-year follow-up after the tension-free vaginal tape procedure. Am J Obstet Gynecol. 2011 Nov;205(5):496.e1–5; Olsson I, et al. Long-term efficacy of the tension-free vaginal tape procedure for the treatment of urinary incontinence: a retrospective follow-up 11.5 years post-operatively. Int Urogynecol J. 2010 Jun;21(6):679–683; Liapis A, et al. Long-term efficacy of tension-free vaginal tape in the management of stress urinary incontinence in women: efficacy at 5- and 7-year follow-up. Int Urogynecol J Pelvic Floor Dysfunct. 2008 Nov;19(11):1509–1512; Svenningsen R, et al. Long-term follow-up of the retropubic tension-free vaginal tape procedure. Int Urogynecol J. 2013 Aug;24(8):1271–8; Chêne G, et al. Long-term results of tension-free vaginal tape (TVT) for the treatment of female urinary stress incontinence. Eur J Obstet Gynecol Reprod Biol. 2007 Sep;134(1):87–94; Bjelic-Radisic V, et al. Patient-related Outcomes and Urinary Continence Five Years After the Tension-Free Vaginal Tape Operation. Neurourol Urodyn. 2011;30(8):1512–1517; Wu JY, et al. Surgical therapies of female stress urinary incontinence: experience in 228 cases. Int Urogynecol J. 2010 Jun;21(6):645–649; Song PH, et al. The 7-year outcome of the tension-free vaginal tape procedure for treating female stress urinary incontinence. BJU Int. 2009 Oct;104(8):1113–1117; Kuuva N, Nilsson CG. Long-term results of the tension-free vaginal tape operation in an unselected group of 129 stress incontinent women. Acta Obstet Gynecol Scand. 2006;85(4):482–

487; Celebi I, et al. Results of the tension-free vaginal tape procedure for treatment of female stress urinary incontinence: a 5 year follow-up. Arch Gynecol Obstet. 2009 Apr;279(4):463–467; Prien-Larsen JC, Hemmingsen L. Long-term outcomes of TVT and IVS operations for treatment of female stress urinary incontinence: monofilament vs. multifilament polypropylene tape. Int Urogynecol J. 2009 Jun;20(6):703–709; Jelovsek JE, et al. Randomized trial of laparoscopic Burch colposuspension versus tension-free vaginal tape: long-term follow up. BJOG. 2008 Jan;115(2):219–225; McCracken GR, et al. Five Year Follow-up Comparing Tension-Free Vaginal Tape and Colposuspension. Ulster Med J. 2007 Sep;76(3):146–149.)

The incidence of mesh exposure is low, but varies in studies between 1 and 5%. A short version Cochrane Review in 2011 observed that the monofilament synthetic midurethral slings—such as the TVT, TVT-O, TVT-Abbrevo, and TVT-Exact—were more efficacious and were associated with a lower rate of erosion than multifilament non-type-1 meshes. (Ogah J, Cody DJ, Rogerson L. Minimally invasive synthetic suburethral sling operations for stress urinary incontinence in women: a short version Cochrane review. Neurourol Urodyn. 2011 Mar;30(3):284–91.) Mesh exposure is usually asymptomatic, can cause a vaginal discharge and possibly cause coital discomfort in the male partner. Management can be topical application of vaginal estrogen or excision under local anesthetic in the office. Removal of the exposed mesh can still provide continence 80–90% of the time. (Klutke C, et al. Urinary retention after tension-free vaginal tape procedure: incidence and treatment. Urology. 2001 Nov;58(5):697–701.) While mesh-related complications can occur after placement of a polypropylene sling, the rate of such complications is acceptably low. The rate of reoperation has consistently reported to be approximately 2–5% for voiding dysfunction and exposure after a decade or more of follow-up in various studies, meta-analyses, and database reviews. (Welk B, et al. Removal or Revision of Vaginal Mesh Used for the Treatment of Stress Urinary Incontinence. JAMA Surg. 2015 Dec;150(12):1167–75; Unger CA, et al. Indications and risk factors for midurethral sling revision. Int Urogynecol J. 2016 Jan;27(1):117–22; Schimpf MO, et al. Sling surgery for stress urinary incontinence in women: a systematic review and metaanalysis. Am J Obstet Gynecol. 2014;210:1.e1–1.e27; Laurikainen E, et al. Five-year Results of a Randomized Trial Comparing Retropubic and Transobturator Midurethral Slings for Stress Incontinence. Eur Urol. 2014 Jun;65(6):1109–14; Jonsson Funk M, et al. Sling revision/removal for mesh erosion and urinary retention: long-term risk and predictors. Am J Obstet Gynecol. 2013 Jan;208(1):73.e1–7; Svenningsen R, et al. Long-term follow-up of the retropubic tension-free vaginal tape procedure. Int Urogynecol J. 2013 Aug;24(8):1271–8; Nguyen JN, et al. Perioperative complications and reoperations after incontinence and prolapse surgeries using prosthetic implants. Obstet Gynecol. 2012 Mar;119(3):539–546; Ogah, J., Cody, JD, Rogerson, L. Minimally invasive synthetic suburethral sling operations for stress urinary incontinence in women. Cochrane Database Syst Rev. 2009 Oct 7, Issue 4. Art. No.: CD006375. doi: 10.1002/14651858.CD006375.pub2; Novara G, et al. Complication Rates of Tension-Free Midurethral Slings in the Treatment of Female Stress Urinary Incontinence: A Systematic Review and Meta-Analysis of Randomized Controlled Trials Comparing Tension-Free Midurethral Tapes to Other Surgical Procedures and Different Devices. Eur Urol. 2008 Feb;53(2):288–308.)

V. The TVT, TVT-O, TVT-Abbrevo, and TVT-Exact Instructions for Use and Other Educational Materials

a. Ethicon's Instructions for Use

The instructions for use (IFU) included with the devices are specific in detail to allow the safe deployment of the devices. The procedures are adequately described such that a trained and experienced physician could implant the devices safely and effectively. The indications are adequately described in terms of patient selection and contraindications for surgery. The contraindications and warnings are adequately described based on my experience and review of the literature. The IFU is not intended to teach surgical technique, which is assumed to have been in the skill set of the surgeon. Every pelvic surgeon should be aware of the intraoperative and post-operative risks inherent. A surgeon need not be taught the entire practice of medicine in an IFU. The totality of surgical risks of pelvic floor surgeries is not included in the IFU for gynecologists or urologists and does not need to be, as the risks of anti-incontinence surgery are commonly known to surgeons. (21 C.F.R. Part 801(c); FDA Device Labeling Guidance #G91-1 (blue book memo); Ethicon Franchise Regulatory Labeling Guidance § 6.1.2 ("Labeling must convey the information that end-users need to safely use the device as intended by the manufacturer, taking into account the conditions of use and any issues that may be specific to the type of device.") Surgeons have training from numerous sources—medical school, residency, maybe fellowships, colleagues' experiences, their own experience, literature, etc.—all of which provide information regarding the risks of incontinence treatments specifically or surgery in general. (Accreditation Council for Graduate Medical Education Program Requirements for Graduate Medical Education in Female Pelvic Medicine and Reconstructive Surgery Pt. IV.A.5.b).(2).(c) (noting that fellows completing the F2 year must demonstrate competence in their knowledge of indications, contraindications, limitations, complications, techniques, and interpretation of results of screening, diagnostic, and therapeutic procedures including surgery for pelvic organ prolapse and urinary incontinence); AUGS Resident Learning Objectives (noting that residents should understand the benefits, risks, and expected outcomes of nonsurgical and surgical management of SUI); American Board of Obstetrics and Gynecology, Inc. Guide to Learning in Female Pelvic Medicine and Reconstructive Surgery 2012 (noting that fellows will perform and describe the indications, intra and postoperative complications, and success of incontinence procedures including synthetic retropubic and transobturator slings).) The IFU is used by the surgeon to become familiar with the specific device, the handling, placement and deployment in the manner that maximizes safety and efficacy. The IFU is never assumed to be a completely comprehensive list of all the possible adverse complications that are low prevalence. The IFU is intended to guide the surgeon to perform the procedure as the device was designed.

Mesh exposure and erosion are the only unique risks to mesh surgeries, and are essentially wound complications. Wound complications can also occur with other surgeries. Mesh exposure can be caused by poor quality tissue due to atrophic vaginitis, history of pelvic radiation therapy, too superficial dissection prior to sling placement, hematoma, and early sexual activity. The IFUs advise surgeons that:

- Failure to follow instructions may result in improper functioning of the device and may lead to injury.
- It's not a comprehensive reference to surgical technique for treating SUI.
- The device should only be used by physicians trained in the surgical treatment of SUI and specifically in implanting the device.
- All information should be read carefully prior to performing this procedure.

The IFU package insert is included with each device and is used as a guide for the surgeon to use the device in the manner it is intended. The IFU lists indications for use, contraindications, most prevalent risks, and the detailed description of how to deploy the device safely. IFUs in general are not intended to list every possible adverse event or post-operative complication. The IFU is generally understood to be a guide in the proper deployment of the device. Surgeons are trained in residency how to manage vaginal surgery with anatomy, handling of tissues, defining surgical planes, and perioperative care. The IFU functions to describe how this particular device is best deployed, but the patient selection, preoperative informed consent, perioperative management, and post-operative care of the patient is the surgeon's responsibility. The patient's degree of severity of vaginal prolapse and stress incontinence, with consideration of patient age, tissue integrity, previous pelvic surgery, health status, tobacco usage, and steroid or opioid dependency leads the surgeon to make a complex decision about surgical approach and the likelihood of success.

b. Ethicon's Training Programs

Ethicon began offering didactic training programs for the TVT in 1999 and later for pelvic prolapse repair when both Gynemesh and Prolift became available. The programs include didactic lectures followed by hands-on cadaver labs with experienced pelvic surgeons at each cadaver station guiding the use of the devices with step-by-step instructions about the use of the products. The didactic lectures are provided by faculty members invited from academia and private practice with extensive backgrounds in pelvic surgery and the use of Ethicon products. The programs include discussions about disease state, indications for surgery, contraindications, avoidance of complications, and the safe use of the products. Every course included a discussion of management of complications and questions from the audience. Webinars, and telesurgery programs were also offered for surgeons that previously attended cadaver labs, or were for advanced users to become familiar with the newer devices, and for dissemination of information on longer-term results when new papers were published. The preceptors are independent of Ethicon, are required to teach the courses in compliance with the slide set provided so as not to advocate or discuss any off-label uses of the products. I began as a preceptor in 2000 with the TVT and later TVT-O, TVT-Abbrevo, TVT-Secur, Prolift, and Prosima devices. I was thoroughly familiar with the products having performed the surgeries in my own practice. Contributing as a preceptor is professionally fulfilling, as it requires that I remain current in the field, and have the opportunity to collaborate with experts both nationally and internationally. There is a lack of opportunity for surgeons to learn and train on new technologies outside of residency, and Ethicon provided resources that are much appreciated by those pelvic surgeons who would like to stay current and improve their patient outcomes. Each course collected anonymous questionnaires and feedback from the attendees rating the quality of the course and proctors, including whether they felt there was commercial bias. Overwhelmingly, the response

was positive, and those proctors that were not received well were disinvited to teach future courses. The faculty has the opportunity to discuss surgical techniques and management of possible complications prior to each course.

Even after a surgeon attends a course, no certification can be provided that will ensure credentialing at their respective hospitals. Each hospital has a surgery committee that reports to the credentials committee that grants privileges for specific procedures. Surgeons must demonstrate previous training through residency, and the quality assurance department will track patient outcomes and complications. Hospitals vary in their requirements for credentialing, which includes proctoring and/or close surveillance of outcomes for new technologies or procedures. The medical device industry can provide education and training, but does not grant privileges for the use of their products. Surgeons are granted privileges based on the background training, residency director recommendations, and review of malpractice history and National Data Bank files. When credentials committees grant privileges for a specific area, they will not state specific proprietary procedures, but rather generalized areas such as cystourethropexies rather than MMK procedures or the Burch procedure.

c. Ethicon's Patient Brochures

Ethicon's Patient brochures provide information about the medical condition of incontinence, the different types, and treatment options ranging from behavior modification with pelvic exercises, electrical stimulation, medications, and bulking agents, to surgery. The information provided gives general terminology of the disease state, possible causes, and symptoms, as well as diagnosis and treatment options. The brochures are not intended to be in-depth and comprehensive, but rather to serve as a reference along with the website to pursue further information if desired. A list of contraindications for surgery is also included. The description of the procedure includes the most frequently encountered possible adverse events and repair options. The brochures are not intended and have never been used in my practice to serve as the only source of preoperative informed consent. Patients are separately informed about the indications, alternative treatments, and description of how the mesh sling will be implanted. Risks of bleeding, infection, bowel or bladder injury, persistent incontinence, retention, and pain are discussed. The possibility of mesh exposure or erosion is also discussed with re-operative repair techniques or application of vaginal cream. The information clearly states to discuss any questions with the surgeon and also provides a toll-free number to call to discuss questions with an on-call nurse.

VI. The Design of the TVT, TVT-O, TVT-Abbrevo, and TVT-Exact Devices

a. The Usefulness, Desirability, and Safety of the Devices

Prior to the availability of the TVT family of products in the U.S., surgery for stress incontinence had been more morbid and less predictable in surgical treatment outcomes. Patients who have undergone open suspensions such as a Burch procedure that have failed are reluctant to undergo reoperation due to the long and painful recovery from the open repair. Surgeries that attempt to pull up and fix the urethra and bladder neck to the pubic bone require a more extensive surgical dissection, which increases blood loss, operative time, require larger incisions,

and could cause damage to the neurovascular support of the bladder neck and urethra. Suspending procedures such as the Stamey, Peyrera, and Raz needle suspensions have been abandoned over the years due to high failure rates. The introduction of a new theory of continence by Petros and Ulmsten in the 1990s, called the integral theory, changed the approach to continence from obstructive to stabilizing the bladder neck and urethra.

The TVT, TVT-O, TVT-Abbrevo, and TVT-Exact slings are implanted via tiny incisions and the mesh slings are placed under no tension. The procedures can be performed as an outpatient under local anesthesia. The procedures do not routinely require catheterization post operatively, and can be routinely performed in under 30 minutes. Continence can be tested during the procedures. They are outpatient procedures with discharge in 3–4 hours. There is little pain, and many patients do not even need pain meds. Persistent or chronic pain occurs rarely. A recent systematic review and meta-analysis indicated that persistent or chronic pain occurs in 0.3% of retropubic midurethral sling patients, and 1.2% of trans-obturator midurethral sling patients. (Tommaselli GA, et al. Medium-term and long-term outcomes following placement of midurethral slings for stress urinary incontinence: a systematic review and metaanalysis. Int Urogynecol J. 2015 Sep;26(9):1253–68.) Most women can drive a car the next day, resume working within two days, and return to normal exercise in just one week. The large pore size allows rapid tissue incorporation and is anchorless, which decreases post-operative pain and voiding dysfunction. Because there are no anchoring sutures or fixation screws, there is no possibility of local bone pain or infection. The design of the covering sheath provides protection to the mesh during deployment and de-tensioning, reducing the risk of infection and distortion of the sling. The technique has a quarter-inch incision in the vagina requiring one suture to close and two exit puncture sites that can be sealed with a Band-Aid.

The success rates for TVT are consistently 80–95% with studies carried out up to 17 years. TVT can be performed safely in women of advanced age, and is the ideal procedure for previously failed incontinence surgeries and even the most severe Type 3 intrinsic sphincteric incontinence. The midurethral slings can be deployed either retropubic or transobturator, providing a versatility that expands the indications for use. Either approach avoids an abdominal incision and extensive surgical dissection required by fascial slings and the Burch procedure.

The mesh used in the TVT, TVT-O, TVT-Abbrevo, and TVT-Exact devices is a macroporous polypropylene monofilament knitted weave that is soft, elastic, and well-tolerated by the body, which incorporates the material and becomes a permanent support structure that allows fibroblastic and collagen deposition to provide a new neoligament supporting the mid urethra. The polypropylene monofilament has been safely used in surgery as suture throughout the body for over 40 years, and has been shown to be stable and does not degrade in the body over time. Implantation of the TVT, TVT-O, TVT-Abbrevo, and TVT-Exact is easy to teach and readily learned by both residents and experienced surgeons with reproducibility. Furthermore, the popularity of the devices has led to a greater number of Urologists and Gynecologists offering incontinence treatment to an increasing number of women.

Unlike the Burch or fascial sling, the TVT family of products come with instructions for use, a tracking lot number for safety and batch analysis, as well as MDR reporting and FDA analyses. The devices are not met with cultural or religious objections like allografts or

xenografts, and are extremely effective and durable with very low recurrence rates in patients aged 30–80 years. There is a positive net effect on overactive bladder symptoms with improvement in one-third to one-half of patients after TVT. Additionally, there is a net positive effect on sexual function—no more urinating during intercourse and consistent improvement in validated quality-of-life questionnaires. A 2012 study with 2-year follow-up that looked at sexual function and activity following midurethral sling placement reported significant improvements in sexual function after both retropubic and transobturator sling procedures. Dyspareunia, incontinence during sex, and fear of incontinence during sex all improved significantly after surgery. (Zyczynski HM, et al. Sexual activity and function in women more than 2 years after midurethral sling placement. Am J Obstet Gynecol. 2012 Nov;207(5):421.e1–6.) In fact, one recent systematic review and meta-analysis found that dyspareunia following implantation of retropubic and transobturator midurethral slings was rare. (Schimpf MO, et al. Sling surgery for stress urinary incontinence in women: a systematic review and metaanalysis. Am J Obstet Gynecol. 2014;210:1.e1–1.e27.)

TVT has more RCTs and long-term data than any other incontinence treatment. The TVT, TVT-O, TVT-Abbrevo, and TVT-Exact are easily studied, patients can be counseled on the vast data, and the study data can be compared to other products and surgical approaches. It is comforting as a surgeon to be using a product that is known to have the largest amount of peer-reviewed data from multiple institutions substantiating a safe, reliable, reproducible technique and material. Prolene has been around for 50 years, been safely used in various applications, and the body's reaction to the material is known. Moreover, surgeons desire polypropylene slings, as over 90% of meshes for SUI are polypropylene. The favored approach is transvaginal, midurethral, and supported by all the specialty societies.

The design optimizes safety by avoiding the large abdominal incision needed for a Burch and fascial sling: a 1.5-cm vaginal incision compared to a 6- to 8-inch abdominal incision for a Burch, or multiple incisions for a fascial sling. The trocars used to pass the sling are tapered with a blunt tip so as to pass through the tissues atraumatically as compared to Stamey needles, which are sharper. Passage of the trocars through the retropubic space has been performed for 50 years, and surgeons are familiar with the anatomy. Complications are usually surgery-related and not mesh-specific. Bladder injury occurs in less than 5% of patients, and occurs as a result of trocar passage, which is managed by re-passage of the trocar and placement of a catheter for 24 hrs. The bladder puncture heals rapidly and completely. Plaintiffs' experts may contend that the trocars are passed "blindly" and that that is unsafe. But the use of cystoscopy insures that the trocar passages have not perforated the bladder. Multiple cadaver studies show that with proper technique, trocars are passed within an anatomic margin of safety. The design of the helical passers used with the TVT-O and TVT-Abbrevo is such that it avoids neurovascular structures. Furthermore, bladder and bowel perforation can occur with the Burch procedure or fascial sling procedures as well. I have directly observed post-Burch bladder perforations of the sutures causing infection, bleeding, and stone formation.

Exposures are uncommon and manageable, occurring in about 1–3% of cases. The cause can be poor tissue integrity caused by estrogen deficiency, delayed wound healing due to diabetes, steroid usage, hematoma formation, or placing the sling too superficially. Treatment includes application of topical estrogen cream, re-closure of the mucosal edges, and limited mesh

excision if necessary. The excision can be performed in an office setting under local anesthesia or under light sedation in an OR. Dyspareunia is rare because the slings' design positions the mesh placement under the midurethra, via the distal anterior wall incision, at a part of the vaginal wall where the forces and stress from penile contact are minimal. And the design of the TVT and TVT-Exact provides for the mesh sling to traverse up (vertically) away from the vagina, while the design of the TVT-O and TVT-Abbrevo provides for the mesh sling to traverse laterally away from the vagina.

Obstructive voiding dysfunction occurs in less than 10% of cases and can be readily managed by either opening the incision in the first few days and loosening the sling or waiting 3–4 weeks to incise the sling under local anesthetic. Continence is preserved 90% of the time. Contrarily, an obstructive Burch procedure will require opening the abdominal incision and taking down the previous repair which entails a more morbid and protracted recovery with probable recurrent incontinence.

Infection is extremely rare due to the macroporous mesh allowing the immune cells—macrophages—to remove possible bacteria. (Ford AA, Rogerson L, Cody JD, Ogah J. Mid-urethral sling operations for stress urinary incontinence in women. Cochrane Database Syst Rev. 2015, Issue 7. Art. No.: CD006375. doi: 10.1002/14651858.CD006375.pub3.) Fibroblasts and blood vessel incorporation allow for tissue regeneration and incorporation of the mesh into the body. Due to the permanence of the sling, recurrent incontinence is uncommon. The inert nature of polypropylene avoids the risk of rejection and infection, which can occur with allografts and xenografts. Since the material is not biologic, there is no risk of virus or prion transmission.

Single-incision and mini slings—while appropriate, safe, and effective devices under certain circumstances—have less efficacy and far less data to support their use over full-length slings. Multifilament mesh has been previously established to be poorly tolerated by the tissues with an unacceptable infection and encapsulation rate. Larger pore mesh does not have the same support characteristics, and does not have supporting data to prove equivalence with the established Ethicon mesh that has 17-year published follow-up.

As discussed above, laser-cut mesh has no clinical difference when compared to mechanical-cut mesh in the physiologic range of stress when implanted in the female pelvis. (ETH.MESH.01784823–28 (CER Laser Cut Mesh); ETH.MESH.01222075–79 (Elongation Characteristics of Laser Cut Prolene Mesh for TVT); ETH.MESH.06696367–79 (Performance Evaluation of TVT U Prolene Mesh); Lin AT, et al. In Vivo tension Sustained by Fascial Sling in Pubovaginal Sling Surgery for Female Stress Urinary Incontinence, J Urol. 2005 Mar;173(3):894–897.) The only difference is aesthetic, and any particles lost on mechanical-cut mesh cause no harm, as it is the same Prolene used in suspension procedures, Burch or fascial sling fixations.

All surgical procedures have inherent risks. All pelvic surgeries have similar risks, and the introduction of the TVT family of products served to decrease complications when compared to previous techniques. Because native repairs and cystourethropexies do not involve a kit product, complications are not reportable to the MAUDE database. Scientific research has

provided improved materials and applications to both improve efficacy and decrease complications. Synthetic mesh that is microporous or too macroporous has proven to be either less safe or less efficacious. If the mesh is too lightweight or too large pore, there is inadequate support.

Ethicon has taken extensive steps to ensure the proper use of its products. The IFU, Surgeon's Monograph, Professional Education training, including didactic lectures and cadaver labs, proctorships, and webinars were designed to offer an extensive resource for the pelvic surgeon to learn the indications for use, surgical technique, and avoidance and management of potential complications. The combination of residency training, previous surgical and clinical experience, and the training resources provided by Ethicon led to many pelvic surgeons gaining expertise in the use of its products, which continues to this day.

All pelvic surgery has similar and inherent risks. Pelvic floor surgeons should be and are aware of the potential complications involved with any surgical treatment of SUI based on a combination of their medical school education, their residencies, fellowships, their experience, their continuing education, and their review of the device's IFU if a device is used. Risks such as infection, scarring, inflammation, bladder damage, bowel damage, ureter damage, nerve damage, injury to vessels, wound complications (such as wound dehiscence, herniation, hematoma, seroma, pelvic abscess, exposure, and erosion), pain, pelvic pain, groin pain, dyspareunia, fistula, anesthetic risks, bowel or bladder dysfunction, failure of the operation, bleeding, death, pulmonary embolism, myocardial infarction, pneumonia, deep vein thrombosis, and need for reoperation are basic elemental surgical risks of any pelvic floor surgery involving mesh. Surgeons understand that these complications can happen, and they also understand that the symptoms can range in terms of severity and duration.

Surgeons are expected to understand the anatomy in which they are operating, and should identify and dissect in safe planes, avoiding inadvertent damage to the organs and vessels contained within the pelvis. The education and training of the pelvic surgeon should be adequate to know the possibility of complications and their avoidance, risks of recurrence and reoperation. Indeed, the development of biologic and synthetic materials was motivated by the high failure rate of pelvic reconstruction due to the weakness of the patients' connective tissue leading to the condition requiring repair. There is an extensive body of medical knowledge in the medical literature discussing the possibility of complications with the use of meshes. Surgeons' prior experience with mesh informs their understanding of potential complications with pelvic floor surgeries, including those involved with mesh devices. While mesh exposure is unique to mesh devices, it is obvious, and it is general knowledge within female urology and urogynecology. The potential injury to vessels and organs caused by trocars is well-known to surgeons, and potential mesh exposure and foreign body reactions are common knowledge.

Furthermore, the FDA issued a Public Health Notification in 2008 regarding the use of synthetic mesh for treatment of prolapse and incontinence. It alerted healthcare practitioners to "complications associated with transvaginal placement of surgical mesh to treat Pelvic Organ Prolapse (POP) and Stress Urinary Incontinence (SUI)." It noted that the complications were rare, but could have serious consequences, and that the "most frequent complications included erosion through the vaginal epithelium, infection, pain, urinary problems, and recurrence of

prolapse and/or incontinence." It also noted that there were "reports of bowel, bladder, and blood vessel perforation during insertion," and that "[i]n some cases, vaginal scarring and mesh erosion led to a significant decrease in patient quality of life due to discomfort and pain, including dyspareunia." This Public Health Notification was yet another source of knowledge for surgeons regarding potential complications associated with synthetic mesh midurethral slings, complementing the TVT, TVT-O, TVT-Abbrevo, and TVT-Exact's IFUs, Ethicon's professional education seminars, and the surgeons' training, education, and experience.

Based upon the analysis above, and on my education, my training, my experience using these products and alternative incontinence treatments, and my reading of the literature referenced above, I believe the TVT, TVT-O, TVT-Abbrevo, and TVT-Exact slings are not defective, but are reasonably safe for their intended use and have a positive benefit-to-risk profile; better than the Burch and native tissue slings. In my opinion, the benefits of the TVT, TVT-O, TVT-Abbrevo, and TVT-Exact slings far outweigh the risks of using the devices. The devices are the gold standard and standard of care for treating stress urinary incontinence. At the time the products were launched, I do not believe they could have been made safer for their intended use. The products were state of the art at the time they were launched, and remain so today.

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